XXI

ELECTRON MICROSCOPIC OBSERVATIONS
ON A GLOMUS JUGULARE TUMOR

J. D. BOYD

J. D. LEVER

AND

A. N. GRIFFITH

CAMBRIDGE, ENG.

The glomus jugulare is now well established both as an anatomical entity[4,5,16] and as the seat of not infrequent tumor formation;[2,3,8,9,15] and other clinical and pathological reports. The precise classificatory status of the tissue which constitutes the glomus jugulare is, however, still uncertain. The histological resemblance of the constituent elements of the glomus and of the carotid body is striking and there is general agreement that there is a relationship between the two structures.[7] Indeed, the resemblance extends beyond that of mere histological similarity for there are several reports on the concomitant presence of tumors that have arisen from glomus jugulare tissue and from the carotid body.[6,13,17] There are, however, certain difficulties in the way of acceptance of a complete identity in ultimate nature between the two organs. Thus, for example, there is a marked discrepancy in their respective times of development. The carotid body anlage can be identified in 13 to 16 mm C.R. length human embryos,[1] and it is well established by the 40 mm stage: but an examination of a large and closely graded series of completely sectioned human embryos and fetuses shows no sign of the glomus jugulare in specimens

up to and including the 150 mm stage. (Griffith and Boyd, unpublished observations). Again the function, or at least the only established function, of the carotid body is that of chemoreception; there is no physiological evidence to suggest that the glomus jugulare possesses this, or, indeed, any other function.[10,17] With our present lack of knowledge on their physiology, the inclusion of tumors of this glomus within the group of so-called chemodectomas, as has been done by a number of investigators, seems to us to be presuming an analogy in function between these structures and the carotid body when the homology between them is still in doubt. Even if the parenchymal cells of the carotid body and of the glomus jugulare prove to be completely homologous it will not necessarily follow that the two structures have equivalent physiological activities though their constituent cells may (for example, as producers of a neurohumor) possess similar or identical functions. The carotid body is not a mere tissue; it is an organ compounded of its characteristic parenchymal cells, afferent and efferent nerve fibres, specialized blood vessels and connective tissue elements. Moreover it is closely related topographically and developmentally with the carotid sinus pressor-receptor mechanism. The glomus jugulare possesses parenchymal cells which are strikingly similar to those of the carotid body, and it also possesses a nerve supply. We are, however, completely ignorant on the nature of this nerve supply; there is no evidence to indicate that the nerve fibres reaching this glomus are either afferent or efferent. There is, also, no indication that a specific pressor-receptor mechanism is associated with any of the arteries related to it.

Finally it should be noted that the clinical pattern of the tumors arising from the carotid body and glomus jugulare shows some marked and unexplained differences. The sex incidence of the carotid tumors is equal, whereas that of the glomus jugulare is about 1 male : 5 female.[2] The carotid body tumors have an equal distribution on the left and right side, but those of the glomus jugulare are reported more frequently on the left in a number of series (Lt. : Rt. 5 : 2 Stuart, Ogilvy and Samon; 4 : 1 Bickerstaff). Guild[5] has reported that normal glomus jugulare tissue is not significantly related to sex or side. There is a bilaterality of carotid body tumors in about 10 per cent, but bilateral glomus jugulare tumors have not yet been reported. Deep x-ray therapy reveals an unexpected radiosensitivity of the glomus jugulare tumor, whereas carotid body tumors are acknowledged to be radioresistant.

In view, therefore, of the indeterminate nature of the evidence linking the glomus jugulare and the carotid body it seemed to us

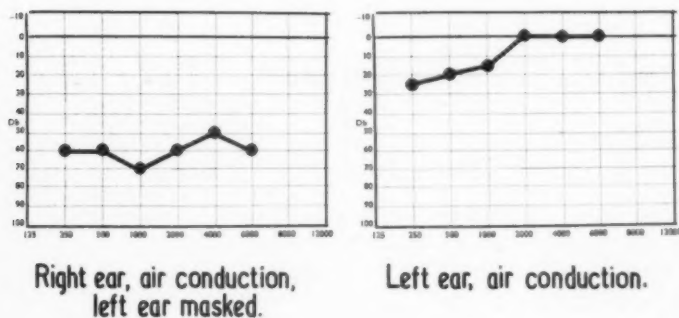**Right ear, air conduction, left ear masked.** **Left ear, air conduction.**

Figure 1

that an electron microscopic examination of material from a tumor of the former might help a little to clarify the relationship. The present contribution reports on such an examintion.

REPORT OF A CASE

Mrs. R. Case No. 77948: admitted to National Hospital, Queen Square, London, May 12, 1958, under the care of Dr. S. P. Meadows.

This patient was a housewife, aged 51, who complained of a nine year history of pulsating noise in the right ear. She had become increasingly deaf in this ear over this period. Six years ago she observed in the mirror that the right side of her tongue was thin and wrinkled. The following year her voice became weak and husky for a time but after a few months it recovered. During the last three years she has found her dress slipping down the right shoulder which appeared to have dropped. At no time has she had any dizziness, giddiness, faintness, change in sensation or loss of weight. She comes from a fit family and there is no significant past medical history.

While in hospital she was referred to Mr. Terence Cawthorne for his otological opinion. She was found to have a severe conduction deafness of the right ear (Fig. 1).

The fundus of the right external auditory meatus was filled by a vascular polypoid mass and some purulent matter. A loud bruit pulsating in time with the heart beat could be heard over the right mastoid process and the whole of the right temporal region of the
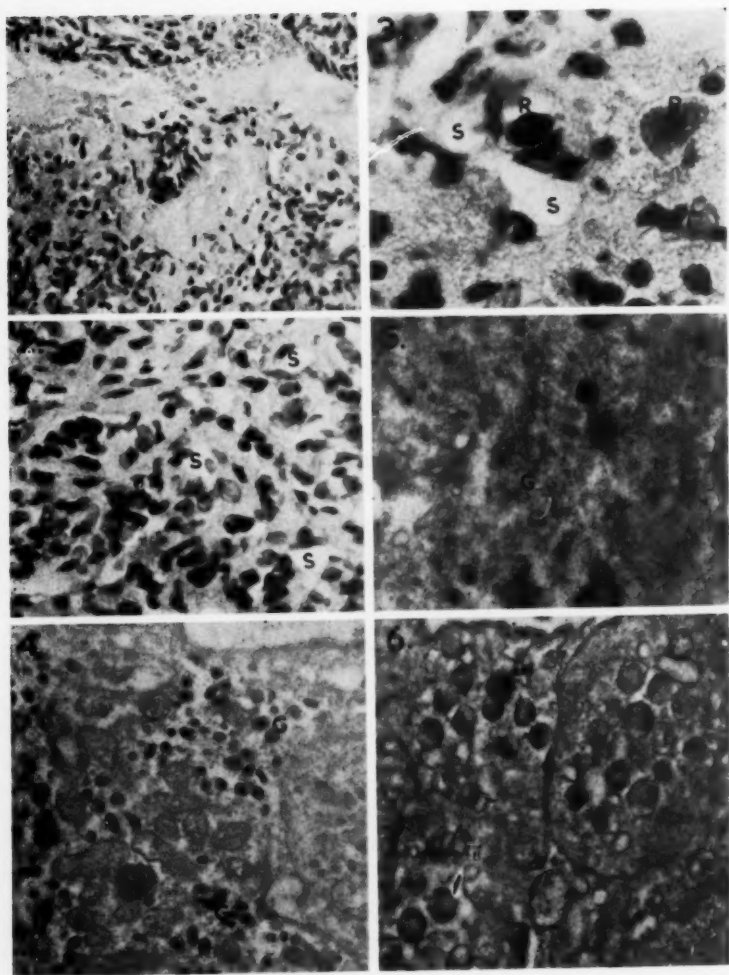
Figure 2

1 to 3 inclusive are light micrographs of an infected polypoid tumor which is seen to be of a glomus jugulare nature: sections stained by hematoxylin and eosin.

Section 1.   Areas of hyaline degeneration and hemorrhage are common. X 280.

Section 2.   The glomus cells appear for the most part degenerate with an eosinophile cytoplasm and pale reticular nuclei: in some locations glomus cells are typically grouped around blood sinusoids (S). Polymorph and round cell infiltration can be observed throughout the tissue. X 500.

Section 3.   Glomus cells may be seen grouped around blood sinusoids (S): glomus cell walls are not easily perceived and their cytoplasm appears eosinophilic, spongy and degenerate. Polymorphs (P) and round cells (R) are commonly seen. X 1040.

Section 4.   An electron micrograph of rabbit carotid body glomus cells showing the presence of intracellular membrane-bound osmiophile granules (G): these range in size from 0.05 to 0.15 μ. X 20,000.

Section 5.   Description and magnification as in 4. The granules at the lower end of the size range are common in the Golgi region (G).

Section 6.   Occasional cell clusters of this appearance are seen within the glomus polyp and often within blood vessels. Their large contained granules range up to 0.3 μ in size, are clearly membrane-bound, and in general resemble the granules of the neutrophile polymorphonuclear leucocytes described by other authors. X 20,000.
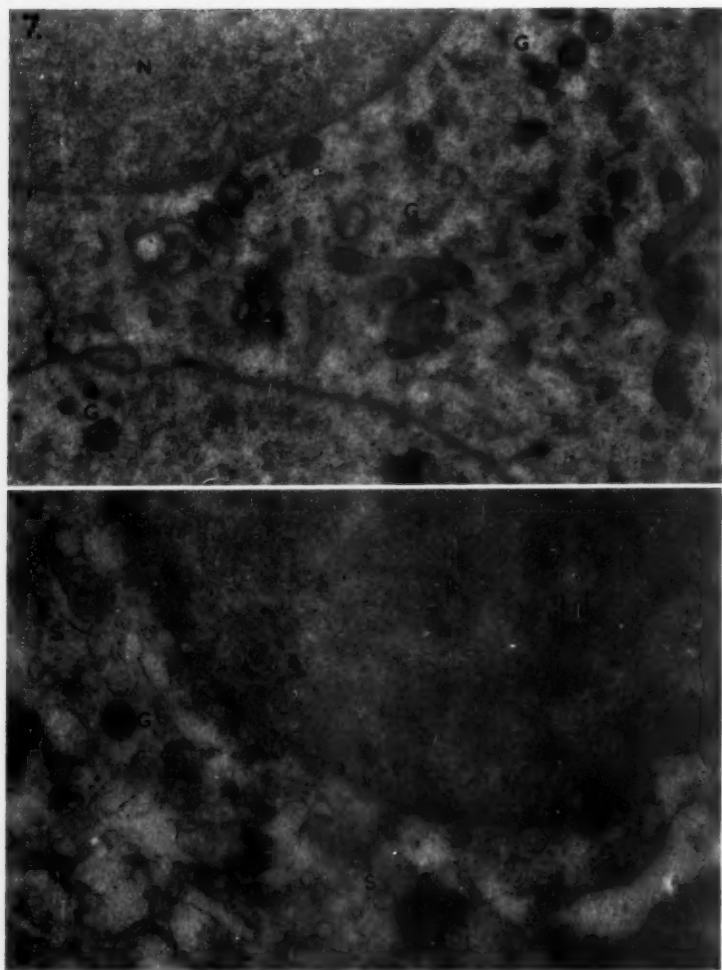
FIGURE 2

Figure 3

Sections 7 and 8 are electron micrographs X 33,000, depicting respectively, portions of rabbit carotid body glomus cells (Sec. 7) and part of an epithelioid cell from the glomus jugulare tumor (Sec. 8). The following lettering is common to both sections: nucleus (N), membrane-bound osmiophile granules (G), cytoplasmic sacs and vesicles (S).

head. Its volume was decreased by homolateral carotid compression and increased by contralateral compression and vasodilator drugs, e.g., amyl nitrite. Other findings on the right side were: a slight weakness of facial movement when smiling; diminution of taste and lachrymation; a palatal and vocal cord paresis; wasting of the sterno-mastoid and trapezius and fasciculation and wasting of the right side of the tongue which was protruded to the right. There was no spon-taneous or positional nystagmus. Caloric tests were not performed on account of the middle ear pathology. Radiographs of the skull were normal but a special view of the petrous temporal bones demon-strated erosion of the right jugular fossa: this was confirmed by coronal tomographs. A biopsy of the polyp proved it to be vascular. There were no other significant findings.

When the diagnosis of a glomus jugulare tumor was confirmed histologically the patient was referred to Mr. T. M. Prosser of West-minster Hospital for radiotherapy.

Materials and Methods. The polyp was subjected to routine hist-ological examination after sectioning and staining with hematoxylin and eosin: representative portions of it were also fixed in Palade's 1 per cent buffered osmic acid, methacrylate-embedded, sectioned and ex-amined by electron microscopy.

Microscopy. Histological examination (Fig. 2, Sections 1, 2 and 3) of the biopsy material stained by hemotoxylin and eosin demon-strated certain features characteristic of glomus tissue: large epitheli-oid parenchymal cells with pale reticulated nuclei were in some situations clustered in cap-like fashion around capillaries or sinusoids (Sec. 2), an arrangement similar to the glomus cell groupings in the carotid body. A negative chromaffin reaction was given in these cells. The tumor was permeated by a highly vascular fibrous stroma and contained areas of hyaline degeneration (Sec. 1). There was a neutro-phile polymorphonuclear and round cell infiltration (Secs. 2 and 3) of the whole polyp but this was particularly marked near areas of surface ulceration. Occasional mitotic figures were seen but there was no evidence of malignancy.

After a great deal of fruitless search with the electron microscope through areas of complete cell degeneration or fibrosis, attention was focused on small groups of epithelioid cells randomly distributed through the tissue, each group lying closely related to a capillary. It was assumed that these cells corresponded to the glomus-like groupings observed with the light microscope. Indeed some of the electron microscopic features of these cells (see below) resembled those pre-
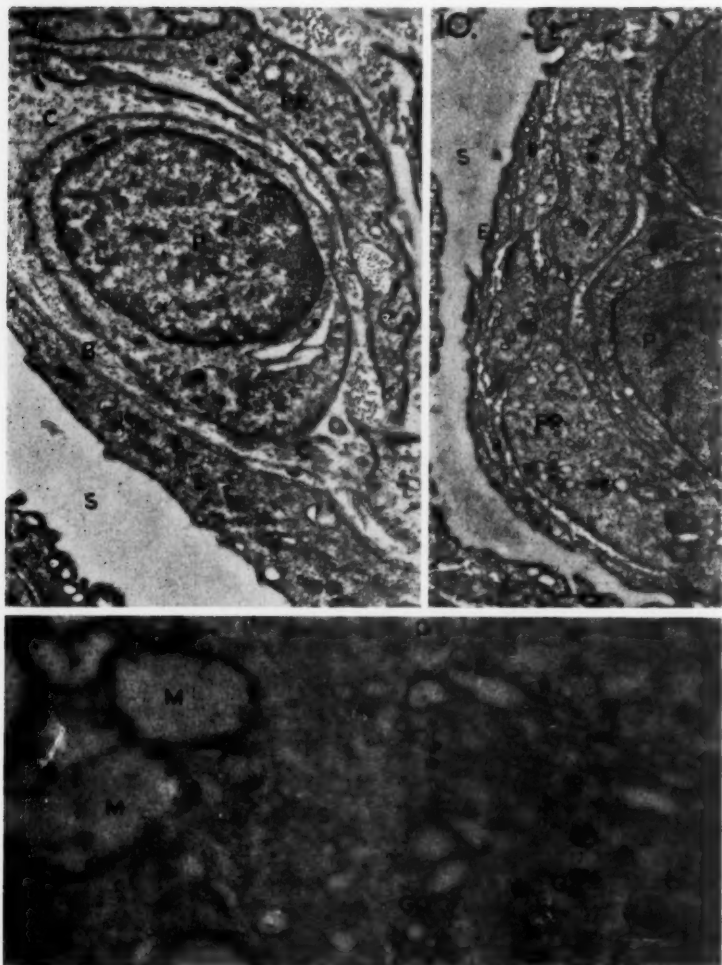
Figure 4

Sections 9 and 10 are electron micrographs X 15,000, depicting a comparable cellular-vascular arrangement observed in both the rabbit carotid body (Sec. 9) and the glomus jugulare tumor (Sec. 10). In both sections a blood sinusoid (S) lined by endothelium (E) is surrounded by a perivascular space lined by a basement membrane (B) and containing besides collagen (C) obvious pericytes (P) or processes of pericytes (PP).

Section 11. An electron micrograph depicting the general cytoplasm and Golgi region (GO) of an epithelioid ("glomus") cell from the glomus jugulare tumor. Note membrane-bound osmiophile granules (G), cytoplasmic sacs (S) and swollen disorganized mitochondria (M). The small granular (R.N.A.) particles of Palade (P) may be seen in relation to the walls of some of the cytoplasmic sacs. X 35,000.

viously reported in the cat and rabbit carotid body glomus cell[11] (also Lever, Boyd and Lewis, in press). It was apparent in these earlier studies that apart from the vascular, nervous and connective tissue cells and constituents in the carotid body, there were at least two further cell types to be considered: firstly the glomus cell itself and secondly a "pericyte" of ambiguous identity which was encountered in a perivascular situation and very probably extended its cell processes to an unknown degree between the glomus cells. Counterparts to both these cell types have been found in electron micrographs of the polyp (and are described below): but in this tumor the tissue organization was not as regular as in the carotid body in respect of cellular-vascular and intercellular relationships.

Although the majority of the epithelioid cells in the polyp were degenerate and quite unphotogenic some were sufficiently preserved to demonstrate cytological details (Fig. 3, Sec. 8, and Fig. 4, Sec. 11). In general these cells resemble what have been described as "light" (glomus) cells in the rabbit carotid body:[11] that is to say, their cytoplasmic matrix is only moderately dense and contains grossly vacuolated and distended mitochondria (Sec. 11). They also have a sparse but conspicuous content of osmiophilic granules (Secs. 8 and 11), ranging in diameter from 0.075 to 0.2 µ: these granules in the polyp epithelioid cells very closely resemble those in the cat and rabbit carotid body glomus cells both in appearance and size range (Secs. 4, 5 and 7): carotid glomus granules measure from 0.05 to 0.15 µ. In both tissues they are bounded by a single membrane and contain a moderately dense microgranular material which in some instances is separated from the enclosing membrane by a space of variable width (Secs. 7 and 8): empty sacs and others only partially filled with granular material are frequently encountered (Secs. 7 and 8). Granules at the smaller end of the size range in both tissues are commonly seen in the Golgi regions of the respective cells (Secs. 5 and 11).

The presence of neutrophile polymorphonuclear leucocytes within the polyp at first caused some confusion since they also contain membrane-bound granules:[14] but these granules are for the most part consistent in size and larger than the glomus cell granules, having a mean diameter of about 0.25 µ (Fig. 2, Sec. 6).

A further comparison is possible between the carotid body and the tumor under examination: in both tissues (Fig. 4, Secs. 9 and 10) there is a cell of ambiguous appearance situated in an immediately perivascular position. In the carotid body it has been termed a "pericyte" (Lever et al, in press) and as already stated, processes from it may be observed insinuated between glomus cells.

SUMMARY AND CONCLUSIONS

So far as the authors are aware there has hitherto been no report on an examination of ultra-thin sections of a glomus jugulare tumor with the electron microscope. The present communication indicates that even with material which is as unpromising from the point of view of electron microscopy as a biopsy from an ulcerating polyp, interpretable micrographs can be obtained. These micrographs, therefore, form in themselves a record of the fine structure which is possessed by the constituent cells of such a tumor. We, however, were particularly anxious to determine if electron microscopic examination of these cells showed any striking resemblance or difference from similar examinations of carotid body cells. Unfortunately as normal human carotid body is not available for electron microscope examination, and as we have not, so far, been fortunate enough to obtain biopsy material from a human carotid body tumor, our comparison has had, perforce, to be made with carotid body tissue from other mammals. On the grounds of species differences alone our observations and comparison must be cautiously interpreted. The *caveat* is all the more necessary as we have compared sections of a pathological tissue with those of a normal organ. Nevertheless, it does seem to us that there are certain points of similarity in electron micrographs between the parenchymal cells of the carotid body and certain groups of cells in the tissue from the glomus jugulare tumor. The presence of membrane-bound osmiophile granules in the cells from both sources, the overlap in size range of these granules in the two types of cells, the fact that in each type the smaller sized granules are located in the Golgi region, are all points of cytological resemblance. Moreover the presence of the pericytes in both carotid body and glomus jugulare add distinctly to the resemblance between them. Until the nature of the osmiophile granules in each structure has been established it would be rash to stress the resemblances too strongly. Our observations, however, seem to add evidence to the opinion that, notwithstanding the difficulties already discussed in the introduction, there is a close cytological similarity between the glomus jugulare and the carotid body.

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XXII

ELECTRONYSTAGMOGRAPHIC STUDIES
OF VESTIBULAR FUNCTION

II.   BASIC PROBLEMS OF CALIBRATION

GODFREY E. ARNOLD, M.D.

AND

FRANCIS MISKOLCZY-FODOR, M.D.

NEW YORK, N. Y.

GENERAL DEFINITIONS

Nystagmography may be defined as a method of permanent registration of ocular nystagmus. Such tracings should present all data necessary for the complete evaluation of nystagmus. Various principles have been proposed for this purpose[17,22,28] which was discussed in a previous paper.[1] As explained by these authors, the electrical methods seem to be most advantageous, particularly the procedure of electronystagmography (ENG) by means of the generally available EEG equipment.

When attempting to measure nystagmus as one sign of a specific vestibular reaction, we have to consider at least the following basic qualities of the complex pattern: 1) latency, 2) amplitude, 3) frequency, 4) direction, 5) binocular co-ordination, and 6) total duration.

Direction and frequency are very easily evaluated from almost any type of tracing as long as it contains time markings. There is also no problem in differentiating the jerking and undulating types of a nystagmus pattern, nor in comparing the movements of both eyes. However, the evaluation of the total duration and of the amplitude may present some difficulties. Recent investigations revealed the importance of considering the velocity of the slow phase because a direct relationship between the cupola deflection and the speed of the slow nystagmus component had been demonstrated.[5]

Clinical procedures of simple subjective observation were concerned mainly with the determination of the total nystagmus duration, attempting to express with some arithmetic approximation the intensity of a given nystagmic pattern. However, several authors demonstrated that the recorded total duration gives only a vague indication of the nystagmus intensity. This represents but one aspect of the entire time-dependent nystagmus pattern by indicating the time difference between the visible starting and end points. Obviously, this time interval alone cannot characterize the events within its limits. As Mittermaier[24] has shown, cases of equal total duration may present differences, either of the frequency or of the amplitude of the nystagmus. Such differences may be clinically important since it is questionable whether a constant relationship exists between frequency and amplitude, especially when different individuals or reactions are to be compared.[21,25,27] These components may be influenced by visual stimulations, such as light, fixation, or accommodation. The extreme dissociation of the nystagmus frequency from the amplitude may be seen during general anesthesia, when conjugate deviation as a result of labyrinthine stimulation is characterized by "infinite" amplitude and zero frequency.

There is another reason why the total duration cannot serve as a fundamental measure of the complete nystagmic pattern: Spontaneous nystagmus with a total duration of days or weeks could not be measured quantitatively until the present time, except by the vague indication of the eye position in "nystagmus degrees."

TECHNICAL PROPERTIES OF EQUIPMENT

Many recent investigations lead us to believe that the assessment of nystagmus intensity must be based on the precise measurement of the amplitude of the individual nystagmic beats. When approaching the problem of determining these amplitudes from a graphic record, one should bear in mind that every type of nystagmogram consists of periodic oscillations. These oscillations or spikes may represent the fast component of the nystagmus, its slow component, or each component may be expressed by a specific form of spike. However, the amplitude of these spikes does not necessarily reflect the amplitude of the eye movements. The graphic translation of the recorded eye movements may depend on various details of electrotechnic procedure. At first we distinguish several main principles which involve either direct or indirect registrations.

1. *Direct and linear registrations* of the eye movements can be obtained, and subsequently measured, on nystagmograms recorded
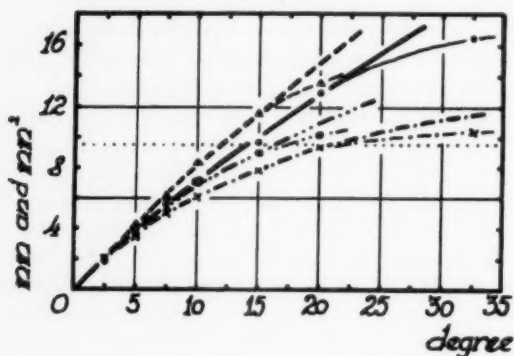
Fig. 1.—Relationship between the angle of induced eye movements and the amplitude (o — . . . — o;   x — . — . — x) or territory (△ — — — — △; ● ———— ●) of the recorded spikes (corneoretinal potential change in the electrodes).   Deviations resulting from nonlinear pen-excursions in the range wider than 9.5 mm are plotted with thin lines.   The dotted line at 9.5 mm is the limit of linear pen-excursion.   Tests performed in dim light revealed smaller corneoretinal potentials (x — . — . — x;   ● ———— ●) than in bright light (△ — — — △;   o — . . . — o).

with linearly functioning mechanical attachments to the eye bulb[10,14] or with photographic techniques.

2. *Linear registrations* may further be achieved with mechano-electrical equipment,[7] and by means of photo-electric procedures.[22,26,28]

3. *Purely electrical*, or electro-electrical registrations translate the recorded eye movements into certain electrical patterns.   These graphic patterns depend on the electric techniques used and must be decoded accordingly.   Many authors advocate the use of electro-electrical registrations which are based on the principle of the corneoretinal potential.[22]   By means of electrodes attached to the skin around the eyes the corneoretinal potential can be picked up.[11,17,24]   The potentials in the electrodes depend on their distances from the electropositive pole (cornea) and the electronegative pole (retina) of the eye. These distances change with movements of the eyes, thereby varying the potentials picked up by the electrodes.   After proper amplification, these changes are graphically recorded.   The significance of the tracing depends on the type of amplifier and time constants used.[3,11,22] Again, we must distinguish two possibilities.

a) The so-called D.C. amplifiers and RC amplifiers with relatively long time constants produce a direct record of the bio-electrical potential. The graphic curve is in linear relation with the angle deviation of the eye.[18,23] Unfortunately, the baseline of these registrations is rather unstable. They also require special electronic attachments or longer time constants than are available in standard EEG apparatus.

b) The so-called A.C. amplifiers, using time constants shorter than the periodicity of the recorded potentials, register only the changes of bioelectrical potentials in the electrodes and not the magnitude of the potential itself. In a mathematical sense, this means the expression of the entire nystagmic movement as a differential of time. It follows that there cannot be a linear relationship between the angle deviation of the eye and the amplitude of the graphic spikes. Instead, the spike amplitude indicates the velocity of the eye movement. For the same reason, the graphic curve returns to the baseline after each eye movement, no matter in what position the eye then remains stationary.[3,9,21] In spite of these limitations, such systems offer a very stable baseline of the tracing. Furthermore the recording of velocity patterns is the basis of certain types of nystagmography.[9]

c) Standard EEG equipment is preferred by many investigators of electronystagmography (ENG). These amplifiers represent capacitance-coupled RC systems and contain time factors which are mostly shorter than the nystagmus periodicity. Tracings obtained with such equipment may be the result of more linear and more differentiated responses which vary with changes of nystagmus periodicity. These tracings may contain a mixture of amplitude and velocity responses, a distortion which interferes with the reliable evaluation of the nystagmus amplitude.

In order to achieve a more linear amplitude response, the time constant should be increased to 1.5 to 2 sec. If, on the other hand, the time constant is kept very short, the tracings will contain mostly velocity patterns.[9]

With these technical possibilities in mind, we arrive at the formulation of the next problem: the evaluation of efficient working conditions by means of standard EEG equipment. Since the standard EEG equipment operates with time constants shorter than 1.0 sec, the further shortening of the time constant in the direction of the velocity-responses appeared suitable for a reliable measurement and analysis of the basic elements of nystagmus patterns. Answers to this problem
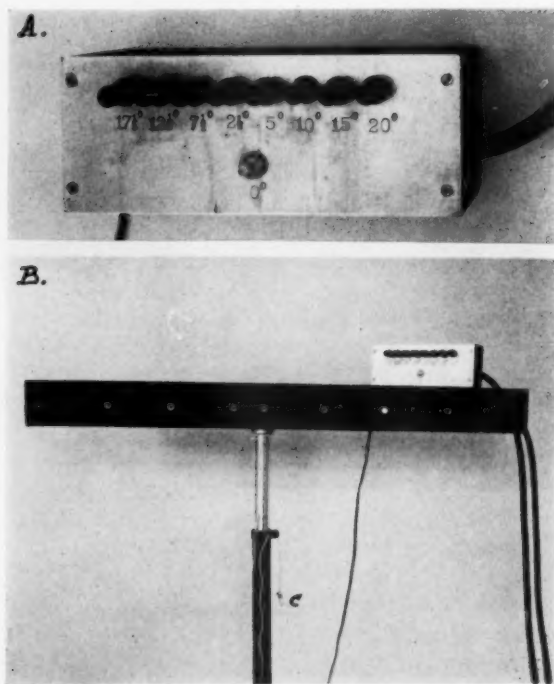
Fig. 2.—Nystagmic gonioscope. A. The switch box contains push but-
tons marked with the degree of induced eye movement to be selected.
B. Gonioscope with portable switch box. The measuring cord (C) indicates
the constant distance from the patient's eyes. At this distance of 55 inches
the lights on the bar induce the specific angle deviations of the eyes. Note
that the light at 10° from the midpoint light is turned on.

will have to consider the following questions: 1) what are the limita-
tions of the registration of velocity patterns? 2) how can one measure
the amplitude of such velocity patterns? and 3) what sources of error
may reduce the reliability of such measurements?

THE MEASUREMENT OF NYSTAGMUS AMPLITUDE

Nystagmographic tracings obtained with standard EEG equip-
ment contain only a derivate of the eye movements. Since they do
not provide a linear reproduction of the eye deviations from position
to position, they are not suitable for a direct measurement of nystag-

mus amplitude. Henriksson[9] developed a system which utilizes the recorded velocity patterns directly for the evaluation of the nystagmus. However, a system based on the computation of the eye amplitude requires a special approach.

If we select short time constants, the interpretation of such tracings requires a computation of the ocular angle deviation from the velocity pattern of the recorded spikes. This method of computation must be practical within the limits of negligible errors. In theory, the mathematical integration of the whole nystagmogram would present the ideal solution. The practice of a clinical test, however, cannot afford so difficult a process. Therefore, we had to clarify the underlying problems of each step of analysis. The basic question concerns the relationship between the graphic velocity pattern and the ocular angle deviation. For this purpose we made investigations on 15 normal persons, recording the ocular potentials evoked by standardized eye movements with well-defined angle deviations.

Method. Since the potentials and their changes recorded from eye movements are in the order of magnitude of radio and TV signals, or of the disturbing electro-magnetic waves produced by various electrical household equipment, provisions must be made for relative electrical silence. This can be achieved by placing the patient in a grounded cage of wire mesh as is often done for electromyographic or EEG registrations.

Attention must be paid also to the stability of the resting corneoretinal potentials. The corneoretinal potential grows with bright adaptation and reaches a stable magnitude after a certain period of time.[2,6] For this reason, the patient should remain in a condition of steady adaptation to light for at least ten minutes before the examination and during its entire course. Modifications of the corneoretinal potentials due to dark and bright adaptation are shown in Figure 1.

As described in the preceding paper, we used silver disc electrodes in various arrangements. In addition to those previously discussed, we also used a different electrode arrangement. By eliminating the nasal electrodes, one may summarize the potentials produced by the lateral movements of both eyes, thereby almost doubling the amplitude of the graphic spikes.[23] Our present binocular arrangement comprises the following electrodes: One above, one below, and one lateral to each eye, with one inactive ground electrode on the forehead.

Again, we made use of the EEG apparatus, Grass Model III D, performing parallel registrations with the time constants of 0.3 (EKG), and 0.05 (EMG), the paper speed being 3 cm/sec.
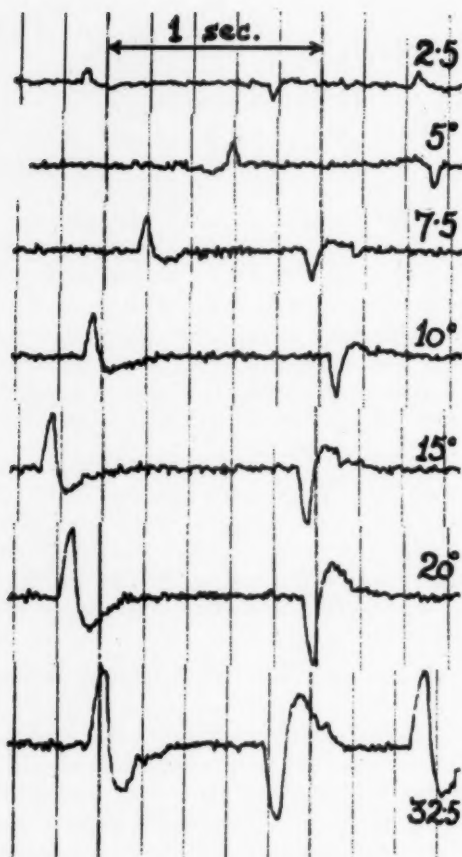
Fig. 3.—Corneoretinal potential changes in bitemporal electrodes record-
ed with standard EEG apparatus and short time constant (0.05 sec). The
different tracings are responses to induced horizontal eye movements of spe-
cific angle deviations. Pen deflections directed upwards indicate an eye devia-
tion to the right side, and vice versa.

Nystagmic Gonioscope. This instrument was devised for the
precise performance of specific eye movements to be recorded and ana-
lyzed. As Guillemin and Torok[28] have shown, the first step of every
ENG tracing is the calibration of the patient's individual physical
responses to known ocular movements. Therefore, we had the follow-
ing gonioscopic device constructed. On a stand of changeable height

is attached a horizontal bar. This contains a row of small electric lights at varying distances from one center light. The distances were calculated in such a way that they correspond to specified angles when the entire apparatus is placed exactly 55 inches from the patient. On the right side of the 'scope the lights are positioned for 5, 10, 15, and 20 degrees of eye deviation; on the left side the distances are arranged for $2\frac{1}{2}$, $7\frac{1}{2}$, $12\frac{1}{2}$, and $17\frac{1}{2}$ degrees (Fig. 2). A portable switch box with push buttons permits the selection of any desired sequence of lights, corresponding to eye deviations from $2\frac{1}{2}$ to $37\frac{1}{2}$ degrees in steps of $2\frac{1}{2}$ degrees. For the sake of convenience, the preceding light combination is automatically turned off as soon as the next angle is selected.

The practical application is very simple. With his head fixed in a head rest, the patient sits comfortably in the wire cage and looks straight ahead at the light in the center of the gonioscope. Next, he is told to follow with his eyes the lights as they appear one after the other. By so doing, his eyes move with a known angle deviation. Hence, the ocular potentials recorded at that time will produce spikes of varying amplitudes. These velocity patterns correspond to the angles selected, and present a known magnitude for further calculations (Fig. 3).

Procedure. For the present investigation we used the following angles of eye deviation from the midline: $2\frac{1}{2}$, 5, $7\frac{1}{2}$, 10, 15, 20, and $32\frac{1}{2}$ degrees.

We further examined whether the initial eye position and the direction of the gaze have any influence on the tracing of the subsequent eye movement. For this purpose we recorded in ten persons the eye deviations of 5 degrees between various starting and end positions of the lights (and therefore of the eyes), namely: 0-5, 5-10, 10-15, 15-20, and $12\frac{1}{2}$-$17\frac{1}{2}$ degrees.

For both directions (to the right and left) of each category of ocular angle displacement, horizontal eye movements were induced 7 to 15 times by lighting the corresponding bulbs. With the first ten patients each eye was recorded with separate electrodes. In the other five cases both eyes were registered jointly by bitemporal leads. Although registrations with longer time constants were recorded simultaneously, we made our computations from the records with the shortest time constant available in standard EEG equipment (EMG: 0.05) for reasons explained above.

The analysis of the nystagmogram was carried out as follows. Each category of induced eye movements with a specified deviation was considered separately. We measured the amplitude (in mm), calculated the triangular space of the spikes (in mm^2), and computed the average results for both horizontal directions of the eye movements (Fig. 4). Since the spikes are similar to triangles, the space content ("territory") of each spike was easily approximated by computing the product of its amplitude and its wave length (in mm) at the base-line which was then divided by two. This equation ($\frac{A \times L}{2}$) appears most reasonable, because the spike amplitude reflects the velocity of the eye movement, and the baseline distance the time. The product
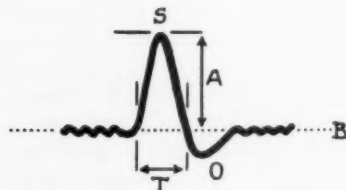

Fig. 4.—Calculation of a "velocity" spike. A voluntary eye movement of 15° was recorded. A = amplitude of the spike, indicating the velocity of the eye movement. T = time duration of the spike at the baseline (B . . . . . .). The territory of the spike ($\frac{A \times T}{2}$) is in linear relation to the angle of the eye movement. S = peak of the spike. O = overexcursion.

of velocity and time should indicate the angular deviation of the eye movement.

Obviously, there must be slight differences between the values of successive spikes of repeated identical eye movements. They result either from variations in the eye movements, or from some errors in measurement. These variations in the measurement of single spikes as a record of ocular movements showed a standard deviation between ± 1.44 and ± 0.18 (centering around ± 0.78) degrees of eye movement. This standard deviation applied to the measurements of both amplitude and territory of the spikes obtained from eye movements over 5 degrees, which is the average excursion of the usual nystagmus beats. It follows that our average results contained a standard error of the mean between ± 0.36 and ± 0.11 (centering around ± 0.18) degrees. Our figures represent summarized results of these averages
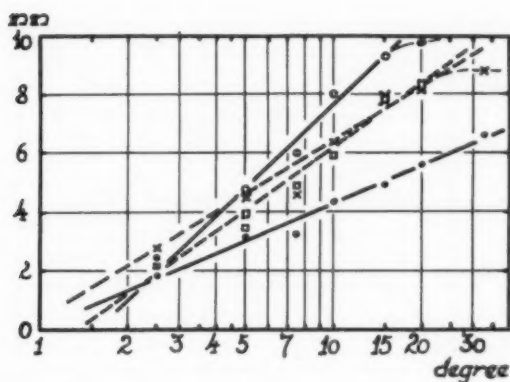
Fig. 5.—CASE V.A. Irregular tracings of intentional eye movements. A logarithmic relationship exists between the angle of induced eye movements and the amplitude of the recorded spikes (velocity). The left eye (— — —) shows similar amplitudes for movements to the right (x — — — x) and to the left (□ — — — □). However, there is a distinct difference in the results of the right eye (—————) between movements to the right (o ——— o) and to the left (● ——— ●). Deviations plotted with thin lines are due to nonlinear responses of the recording pen.

(see next paragraph).   Hence, the standard error of these mean figures is centered around ± 0.13 degree.

COMMENT ON FINDINGS

1) With regard to the different eye positions as a starting point for the induced eye movements, no significant regular differences could be found in the tracings. In other words, it made no difference whether a specified angle deviation, say of 5 degrees, was induced from the midline position, or from an initial deviated position of the eyes.

2) With very few exceptions (cases of squint, after strabismus operation, etc., Figure 5) no significant differences were found in the tracings for eye movements in opposite directions. Therefore, we summarized the results pertaining to eye movements with a specified angle deviation away from the midline or back to it. Thus, we obtained averages for each category of angle deviations.

3) The relationship between the space content of the spikes (territory) and the angle deviation of the eyes depends on the size of the angle: The relationship is much more linear with spike territories,
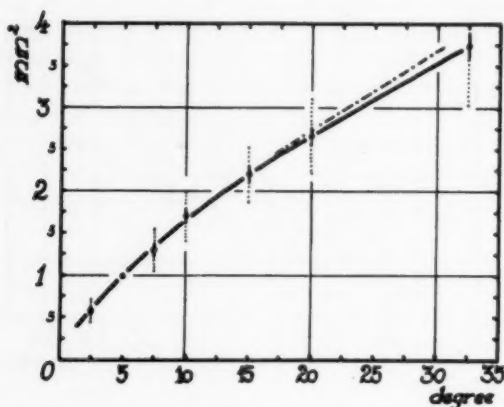
Fig. 6.—Relationship between the angle of induced eye movements and the territory of the recorded spikes as average of 15 tested persons. Vertical full lines: standard error of the mean. Vertical dotted lines: standard deviation of individual measurements. — • — • — Relationship with the sine values of the degrees of eye deflection (abscissa).

than with spike amplitude (Fig. 1). Slight deviations from linearity (Fig. 6) may be caused by at least three interferences: a) distorted pen excursions, b) accessory eye movements, and c) the mechanism of eye rotation.

a) As will be explained later, pen excursions wider than 1 cm failed to follow the signals in a linear manner.[17] (Figs. 1 and 9).

b) In the case of wide eye movements of 20 or 32½ degrees, the induced horizontal deflection was accompanied by marked vertical deviations (Fig. 11). These were registered by vertically applied electrodes which we always included for the detection of such additional palpebral or eye movements. Although this vertical component was part of the entire eye movement, we did not consider it any further, measuring only the tracing of the horizontal deflections. Obviously, a portion of the electric response to ocular movements was then lost to the subsequent computation, which may account for some non-linear results.

c) Finally, we have to consider certain geometric details of eye rotation. When the eye moves sideways, its electro-negative and electro-positive poles do not approach the skin electrodes in a straight
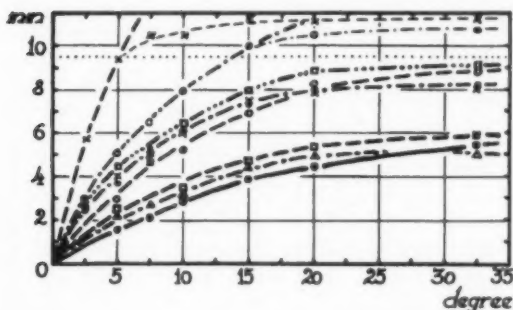
Fig. 7.—Relationship between the angle of induced eye movements and the amplitude of recorded spikes (corneoretinal potential changes in the electrodes) in different tested persons. Horizontal dotted line at 9.5 mm: limit of linear pen-excursion. Nonlinear deviations above this limit are plotted by thin lines.

line because the poles move around a circle. For this reason, the various potentials picked up by the electrodes are not strictly related to the angle of eye rotation, but to the sine of this angle.[15,20,23] Over the range of normal nystagmic eye excursions this difference is without significance. However, it becomes significant, as soon as we consider wider angular deflections (Fig. 6). For instance, with 20 degrees of actual eye rotation, the potential change is expected to be smaller by a half degree than if there were no such sinusoidal relationship; with thirty-two and one-half degrees of eye rotation, the result is expected to be two degrees smaller than it would be if the potential change were related linearly to the angle of rotation (and not to its sine).

4) The amplitude of the spikes as a criterion of velocity attracted our particular interest. It soon became apparent that there cannot be a linear relationship between the angle of eye deviation and the amplitude of the recorded spikes (Figs. 1, 7, 9). Rather, the amplitude of the recorded spikes corresponds to the logarithm of the angle of the induced ocular deviation. We thus arrive at an important deduction: *The velocity of induced eye movements increases with the logarithm of the angle of their deflection* (Figs. 5, 8). Some deviations from this logarithmic relationship in certain cases may be caused by the following influences: a) non-linear distortions introduced by the recording equipment, b) accessory components of eye movements, c) trigonometric relationship between electrodes and eye poles, and d) limitations of the general logarithmic relationship.
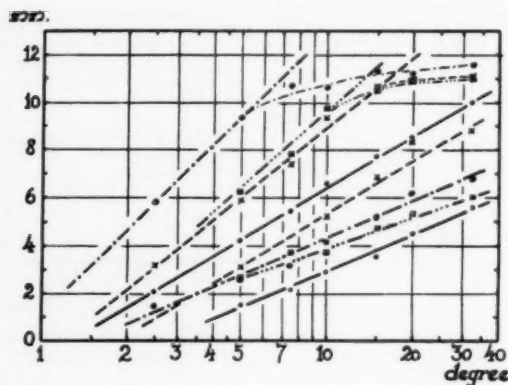
Fig. 8.—Logarithmic relationship between the angle of induced eye movements and the amplitude of recorded spikes (velocity). The logarithmic relation is not affected by changes in amplification. Nonlinear pen-excursions above 9.5 mm are drawn with thin lines. For each tested person two different amplifications were used (plotted with equal symbols).

a) Non-linear distortions of our amplifying and recording equipment began with pen excursions greater than 9.5 mm (Figs. 1, 7, 8, 9, 10; compare also McLay, Madigan and Ormerod). Whenever the amplification exceeded this limit, non-linear responses resulted and this non-linearity was not dependent on any other factors (Fig 9). This decline of linearity was much more apparent in the graphic curves of the relationship with the spike amplitudes, than in those for the spike territory. It is easy to explain this difference by the fact that the triangular space of the spike territory is the product of their amplitude and their duration (in mm). Since the limitation of linear pen excursion influences only the amplitude of the spikes, it becomes less noticeable when the time factor enters the calculation. It is easy to exclude this non-linear distortion by proper calibration procedures. We shall discuss these at a later date.

b) A certain amount of deviation from the strict logarithmic relationship is certainly due to the accessory vertical movements of the eyes in the course of their deflection over wide angular ranges as described above (Fig. 11).

c) The correlation of the recorded potentials with the sine of the angle of eye rotation may account for a certain deviation from the logarithmic relationship as we discussed before (Fig. 6).
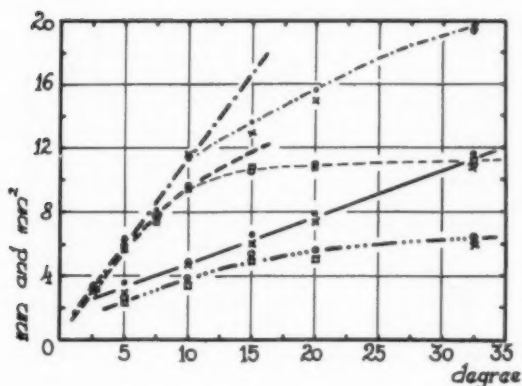
Fig. ·9.—CASE F.S. Nonlinear pen-excursions depend only on the excessive amplitude of the pen. For the same person nonlinear registration is limited to excessive amplification. Relationship between the angle of induced eye movements and the amplitude (— • • • —; — — —) or territory (— • — • — ; ——————) of the recorded spikes. Nonlinear responses due to distorted pen-excursion above 9.5 mm are plotted with thin lines. Symbols: o and ● right eye, x and □ left eye.

d) Apart from these limitations, there remained an occasional slight decline of the values recorded with thirty-two and one-half degrees of eye rotation. We have no explanation for this deviation from the expected values. However, eye excursions of this magnitude are practically never seen in relation to nystagmus. It is therefore superfluous to consider such wide eye movements for the practical purposes of ENG calibration.

Having analyzed the possible causes of certain mathematical deviations, we now arrive at the precise formulation of our observations. Since the territory of the spikes represents the amplitude of the induced eye movements, and since this spike territory revealed a fairly linear relationship with the angle of eye movement (Figs. 1, 6, 9, 10), it can now be stated that *the amplitude of the recorded spikes measures the velocity of the eye movements, if the time constant is significantly shorter than this movement*, or the periodicity of such movement.

Within the range of induced eye movements between two and one-half and 20 degrees of angle deviation, the maximal velocity of the eye movement increases with the logarithm of the angle deviation
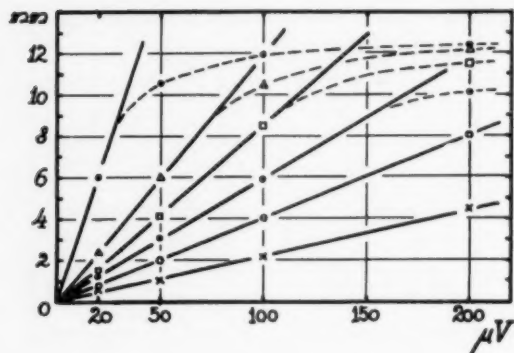
Fig. 10.—Pen-excursion for different internal calibration voltages (abscissa in micro V) for different amplifications (parameters). Pen responses greater than 9.5 mm show marked deviations (— — — —) from linearity.

of the eyes when the nystagmographic record is based on such short time constants.

These relations lend themselves well for the calibration of the recording system. The principle of this calibration is based on the measurement of the amplitude of the recorded spikes. The measured amplitude then presents a standard factor for the quantitative evaluation of the nystagmogram recorded during a given vestibular reaction. Each nystagmogram must contain its own calibration which controls the interpersonal and intrapersonal variations in the corneoretinal potential changes: different persons exhibit varying potentials with identical eye movements; and the potentials of the same person vary at different times. Furthermore, we need the composition of an individual nomogram for the measured amplitudes, keeping in mind that the records obtained with EEG equipment express the velocity of eye movements as a logathrithmic function of their angular displacements.

The angular range of the eye movements usually pertaining to a nystagmus pattern extends from 0 to 10 degrees. In this range the nonlinear relation between the velocity values (spike amplitude) and the angle deviation of the eyes is less noticeable than it is over the range of wider eye deflections. With due caution a linear relationship between the velocity and angular deflection of eye movements may be
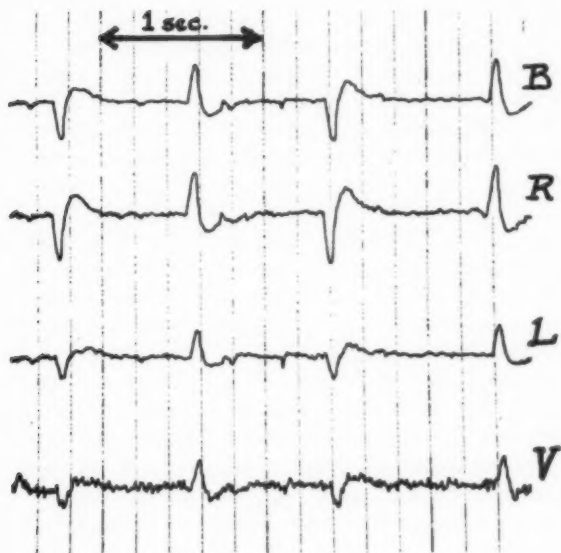
Fig. 11.—Accessory vertical deviation of the eyes during an induced horizontal eye movement of 20°. B = horizontal bitemporal electrodes. R = right eye. L = left eye. V = vertical electrodes. Curve B was recorded with less amplification than R and L curves. Pen deflections directed upwards indicate a horizontal eye movement to the right in the horizontal leads, and an upward vertical eye movement in the vertical leads, and vice versa.

substituted as a practical and permissible approximation. Naturally, this approximation increases the errors of interpretation to a certain degree (Figs. 7, 9). However, these errors do not necessarily exclude the possibility of using an approximative linear relationship in case an investigator should consider the true logarithmic relationship too complicated for his purposes.

CALIBRATION OF EQUIPMENT FOR MEASURING EYE MOVEMENTS

Within the range of nystagmic eye movements, the amplitude of the graphic spikes (velocity) is characterized by a sufficiently constant relationship to the logarithm of the angle deviation during induced eye movements. This fact is used for the calibration of our

recording equipment. It consists in the measurement of the recorded spike amplitudes (in mm) for known induced eye movements.

Procedure. First, the individual responses at a specific time are recorded by means of the gonioscope as described above. This procedure defines the patient's reaction to specified induced eye movements. Next, the spontaneous or reactive nystagmus is recorded with the same electrodes, the same amplification, and through the same channels.

Evaluation. The amplitude values of the spikes resulting from the gonioscopically induced eye movements are plotted in a graph (Fig. 5, 8), which is used as a nomogram. Similarly, the amplitudes of the spikes obtained from the recorded nystagmus are measured in mm. Finally, these amplitude values of the nystagmus tracing are converted into angles of eye deflection by means of the individual nomogram. Thus, the angle deviation of a nystagmic movement can be determined with adequate precision. With regard to the ultimate reliability of the method, two questions should be clarified: one, the differentiation of the nystagmic components; and two, possible differences between induced and compensatory eye movements.

1) *Differentiation of Slow and Fast Component.* According to common knowledge the vestibular nystagmus consists of two different components. The slow movement represents the true vestibular reaction. The fast backrolling of the eyes is due to a central compensating mechanism under the influence of various cerebral regions.

In the ENG recorded with standard EEG apparatus, the spikes represent the fast component of the nystagmus. The slow vestibular component causes a potential change which is partly too slow for a reliable recording, and partly distorted by an over-excursion of the backswinging pen after the fast spike (Fig. 3, 4, 11). Consequently, ENG with this type of tracings is based on the investigation of the fast component of a nystagmus and not on that of the vestibular component.

As long as the fast and the slow component occur with the same angle deviation, the evaluation of the fast component will be applicable also to the slow component. In the course of a vestibular reaction of a normal and fully conscious patient his eyes oscillate in response to the vestibular stimulus. Normally, there cannot exist any prevalence of reactive eye movements in the direction of one of the components (Fig. 9). Therefore, the compensatory fast component must be equal to the angle deviation of the primary vestibular slow com-

ponent. All we have to do then is to compute the averages of several consecutive fast nystagmus jerks. This will exclude a possible difference in angle deviation between some individual nystagmus beats. Different considerations may apply to certain pathologic cases of dissociated nystagmus.

2) *Similarity of Induced and Compensatory Eye Movements.* The calibration as described above was performed with induced voluntary movements. These are obviously not identical with the fast component of a vestibular nystagmus which represents an unconscious reflex. We had to ask next whether this physiologic difference may have any bearing on the relationship between spike amplitude and angle deviation.

When analyzing a voluntary eye movement, we find that only the intention of starting and stopping such a movement can be influenced at will. The performance of the movement itself is considered a reflex action. Under normal conditions it is almost impossible to modify it voluntarily. Brockhurst and Lion[4] found that the maximal velocity of eye movements remained essentially constant throughout an arc of 90 degrees. This velocity could not be reduced voluntarily. Although it is possible to split the total eye movement into several saccadic poritions, each partial motion retains the same maximal velocity.

Since, then, there is no basic difference in the velocity of induced voluntary eye movements and those of the compensatory "back-rolling" of the eye, the ENG system can be calibrated by recording these induced voluntary eye movements. From the resulting calibration values a graph is composed for each test, showing the relationship of the recorded spike amplitude to the known angle deviation of the induced eye movements. This graph serves as a nomogram for the subsequent computation of the nystagmus amplitude (in degrees) from the amplitude of the recorded spikes.

Precautions. Variable individual conditions of skin resistance (usually between 3000 and 10,000 Ohm) and variable anatomical conditions may modify the distribution of the corneoretinal potentials around the eyes. For this reason each test must be preceded by proper calibration which should meet the following requirements: 1) attention to the variability of the corneoretinal potentials, 2) linear pen excursions, and 3) reliable spike amplitudes.

1) *Variability of the Corneoretinal Potentials.* As shown by Aserinsky,[2] François and de Rouck[6] (see above and Fig. 1), the rest-

ing corneoretinal potential is influenced by the adaptation to light.
No change in the resting potential should occur during the period of
calibration and registration.   Otherwise, the amplitude of the record-
ed spikes could be modified by extraneous influences.

2) *Linear pen excursions* are required for the range of eye move-
ments commonly found with nystagmus.   This means that the pen
excursion should not exceed 9.5 mm when recording an ocular
amplitude of 20 degrees in the case of occasional coarse nystagmic
jerks, or an amplitude of 15 degrees in the presence of fine jerks.   As
a rule, eye movements due to nystagmus are in the range of 2 to 8
(or 10) degrees of deviation.   The maximal permissible amplification
of pen excursion (9.5 mm) suffices for the satisfactory recording of
spikes within the angle range of nystagmus.   In general, this amplifi-
cation corresponds to 6 to 7 mm of pen excursion for 100 μV of the
calibrating internal potential pulse in the case of monocular electrodes.
Where bitemporal electrodes are used this amplification corresponds
to 4 to 5 mm for 100 μV.

3) *Reliable Spike Amplitudes.*   The calibration experiment
should not reveal any major scattering of the spike amplitudes.   Hal-
stead[s] was able to reproduce eye movements within a statistical devia-
tion of only ± 1 degree, whereas Jung[11] reported an accuracy of about
± 2½ degrees.   Both authors used A.C. amplifiers.   With the method
as outlined above we arrived at a standard deviation centering around
± 0.78° between individual recorded spikes for the range of normal
nystagmic eye movements.   The average of 5 to 10 spikes for each
eye and each direction, and the summary of these averages of both
eyes and of both directions during induced eye movements revealed
a standard error of the mean centering around ± 0.13°.

SUMMARY

1) When nystagmographic tracings are obtained by recording
the changes of corneoretinal potentials through commonly used ampli-
fier systems, the graphic records contain certain distortions which are
due to the type of apparatus used.   The various amplifier systems
produce characteristic distortions of a specific nature.   In part, these
distortions are due to the time constant of the amplifier.

3) Standard EEG equipment operates with time constants which
are generally regarded as being too short for linear recordings of
nystagmus.   Therefore, we limited our investigation to the study of
a special application of the shortest available time constant (0.05 sec).

3) Studying induced eye movements with specified angle deviation, it was shown that the spikes of the ENG tracing, obtained with standard EEG apparatus, correspond to the velocity of the eye movement. By multiplying the spike amplitude (velocity) with its duration one obtains the territory value of the triangular spikes. These territory values of the spikes show a linear relationship to the angle of induced eye movements. It follows that the spike-territory represents the true substrate of the angle deviation of the eye. Certain deviations are due to specific experimental conditions, as discussed.

4) A logarithmic relationship exists between the velocity (measured from the spike amplitude) and the angle deviation of induced eye movements. This regular relationship presents a suitable method for the calibration of the nystagmographic recording system, including standard EEG apparatus. Thus, the nystagmus amplitude can be determined from the calibrated spike amplitude. The same principle applies also to all other data necessary for the evaluation of the entire nystagmus reaction.

5) Sources of errors, limits of measurement, and the standard deviation of the observations were discussed.

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XXIII

OTITIC MENINGITIS IN THE ANTIBIOTIC ERA:

OBSERVATIONS ON 28 ADULT PATIENTS
TREATED IN THE LOS ANGELES COUNTY HOSPITAL

1950-1957

H. James Hara, M.D.

Los Angeles, Calif.

Persistency of otogenic meningitis in this antibiotic era is a definite challange to the practicing otologist. Inadequacy of chemotherapy, masking of symptoms, and development of drug resistant strains of organisms have been cited as the chief cause of this serious complication.[1] The purpose of this paper is to call attention to the fact that what appears to be a simple middle ear infection, acute or chronic, may lead to a grave intracranial disorder. The practicing otologist must recognize his responsibility in the reduction of morbidity and mortality from this source. In the light of recent advances in the field of chemotherapy and surgery of the temporal bone, the otologist of the present generation should be able to render services hitherto unknown in the annals of medical history.[3]

During a period of eight years from 1950-1957, 66 cases of otitic meningitis in all ages, races and sexes were observed. Thirty-eight of these were children under 15 years of age. Twenty survived and eighteen died, presenting a mortality rate of 47 per cent. The details of a study of these cases will appear in another paper.[2] Of the 28 adults twelve died in the institution. This is a mortality rate of 43 per cent. In the present study the discussion is limited to otogenous meningitis among adult patients. The youngest was 16 and the oldest was 70 years old. All races were represented with a preponderance of Caucasians, corresponding to the racial distribution of the general public in this area. Thus there is no evidence of racial immunity

From Otolaryngologic Service, Los Angeles County Hospital, and the Department of Otolaryngology, College of Medical Evangelists, Los Angeles.
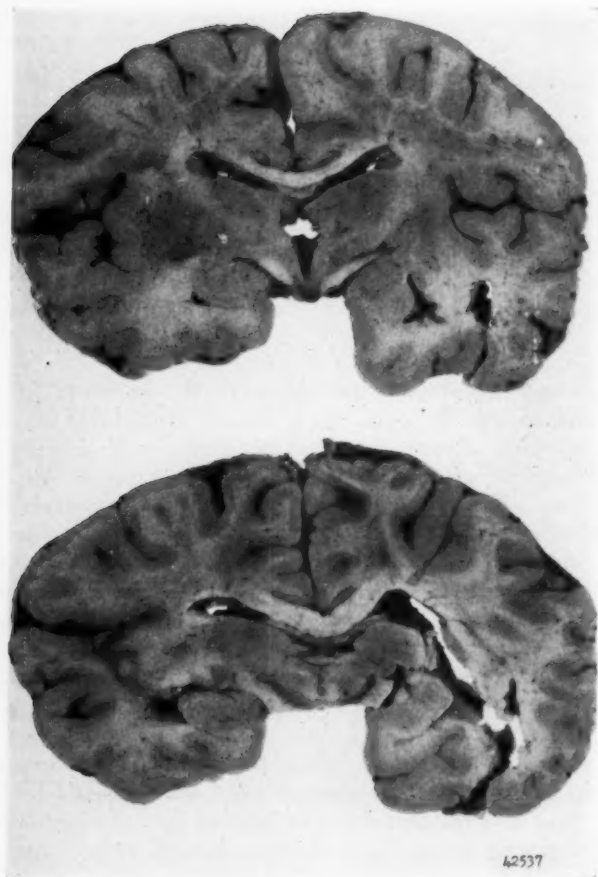
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Fig. 1.—42-537. Two cross sections of cerebral hemispheres. *Top figure*: section through posterior limb of internal capsule shows anterior portion of an acute, unencapsulated abscess of the left temporal lobe. There is no reaction, other than edema, of the regional brain tissue. *Lower figure*: section through midbrain and pulvinar of thalamus. Shows point of entrance of infection on basilar surface of the temporal lobe, its extension into the defect which represents the acute abscess, and subsequent rupture of this abscess into inferior horn of the lateral ventricle.

ACUTE OTITIS MEDIA AND MENINGITIS

There were five who had no previous history of ear diseases but who developed meningitis. Three patients presented histories of head injury and a fracture of the skull 24 hours, six weeks, and three months before their admission. Maxwell,[4] quoting Dandy, stated that head injury and operative trauma are the common causes of spinal fluid leakage. Other factors are inflammation, erosion by tumors and malformation. Again, Maxwell quotes Grove and Nager as saying that a transverse fracture involving the otic capsule has a greater danger of developing meningitis than a longitudinal fracture. However, there are exceptional cases. Chances of recovery in these instances of head injury appear to be proportional to the extent of the trauma and the virulence of the organisms which invade the intra-cranial space. In cases of severe head injury meningitis is a concurrent infection rather than a complication of acute otitis media. The final prognosis depends on the potency of the drugs to stem the tide of infection before the patient succumbs to generalized septicemia and respiratory failure.

REPORT OF CASES

CASE 1. A 58-year-old Caucasian woman sustained an injury to the left side of her face in an auto accident. There was bleeding from the left ear. The next day she was disoriented and was admitted to the contagious diseases pavilion of the hospital in a comatose state. Her spinal fluid cell count was 1200 per cmm. She had a series of convulsions and progressively developed increasing respiratory difficulty. She expired on the same day. Autopsy showed no gross evidence of a skull fracture, but the meninges were highly hyperemic and a thick exudate covered the entire brain. Culture showed pneumococcus.

In the two other traumatic cases their injuries were slight and they survived six weeks and three months and then developed meningitis secondary to acute otitis media. Assumption is that in these instances though there was no radiographic evidence of skull fracture, a sufficient injury to the blood vessels and nerve fibres in the soft tissues had developed. At the subsequent infection the offending organisms found their way into the intracranial structures through the middle ear cleft. Fortunately both of these recovered by a prompt institution of surgical procedure combined with massive multiple chemotherapy and supportive measures. A myringotomy was performed upon one of these patients on admission and a cortical mastoidectomy a week later. His response to chemotherapy was slow. A revision of the mastoid cavity was carried out after four weeks when a recurrent meningitis developed. He ultimately responded to the treatments given and was dismissed 64 days after the initial entry. A modified radical mastoidectomy was performed on the second patient

Fig. 2.—51-752A. The base of the brain showing changes in local meninges on basilar surface of right temporal lobe (left side on photo) where infection entered temporal lobe (dark area). Regional meninges look cloudy as though a meningitis had developed.

and massive antibiotic therapy was instituted. He was discharged as well after 23 days' hospitalization.

In the remaining two cases, the precipitating factor appears to be an upper respiratory infection with a complication of acute otitis media. One survived, the other expired.

CASE 2. A 44-year-old Japanese had contracted a head cold five days before admission. Two days later he developed acute left earaches. This was followed with progressively increasing headaches, fever and nuchal rigidity. He was admitted to the hospital in the state of coma. There were 6600 cells in his spinal fluid. Myringotomy plus antibiotics tipped the scale favorably and he was discharged 25 days after entry.

CASE 3. This patient was a 44-year-old Caucasian with a history of chronic alcoholism. On admission he was in acute respiratory distress with temperature of 104°. There was purulent discharge from the right ear. Shortly after admission he developed convulsive seizures. His course in the hospital was progressively down-

Fig. 3.—51-752B. Cross section of cerebral hemispheres showing entrance into an acute abscess (no capsule) with secondary rupture into inferior horn of right lateral ventricle. Entire hemisphere is swollen from edema.

ward and he expired 31½ hours after admission with acute bronchopneumonia, purulent otitis media, and meningitis.

As demonstrated at autopsy, the most vital factor in the management of these acute otitic complications is in early recognition. The earlier the diagnosis, the better the prognosis. The final outcome depends on 1) the degree of immunity of the hosts, 2) virulence of the organism, 3) their sensitivity to antibiotic chemotherapy, 4) the speed of elimination of both endogenous and exogenous toxins before permanent damage is wrought on the vital centers. To attain this latter objective a myringotomy was performed whenever it was indicated or when one was in doubt; a cortical mastoidectomy in some instances in addition to the institution of multiple antibiotics and supportive measures. We see no advantage in intrathecal medication. In chronic alcoholics, diabetics, and others whose natural immunity is impaired the prognosis should be guarded. Recurrent meningitis msut be promptly dealt with at the first appearance of suggestive symptoms.

CHRONIC OTITIS MEDIA AND MASTOIDITIS

Twenty-three patients in this series of 28 had a history of chronic middle ear and mastoid infection. In four of these either a cortical

Fig. 4.—51-752C. This section through optic thalami shows acute abscess with hemorrhage into surrounding tissues.

mastoidectomy or a radical mastoidectomy was performed at the ages of 7, 16, 21, and 32 years; but the purulent otorrhea persisted with the usual symptoms of chronic mastoiditis.

HEAD INJURIES

Head injuries in those with chronic otorrhea may be a contributory factor in precipitating meningitis. Radiograms may or may not reveal any evidence of a fracture. Trauma, however slight, appears to break the natural line of defense and permits the passage of organisms into the intracranial structures. This may occur immediately at the time of the injury and set up meningitis. In other instances, the antibiotic-resisting organism may remain dormant for several weeks or months. Upon contraction of a fresh head cold the stage then is set again for development of this serious illness. This is the usual course in delayed cases.

CASE 4. A 27-year-old Caucasian married man had a chronically draining ear for more than ten years. He sustained a head injury during a fist fight two months before entry. He developed progressively severe headaches and then a left otalgia two weeks before admission. A possibility of brain abscess was suspected, but ventriculograms proved to be normal. The spinal fluid was turbid and yielded Staphylococcus aureus, coagulose negative. A large amount of cholesteatoma was found during left radical mastoidectomy. His postoperative course in the hospital was stormy but patient was dismissed as well after 62 days.
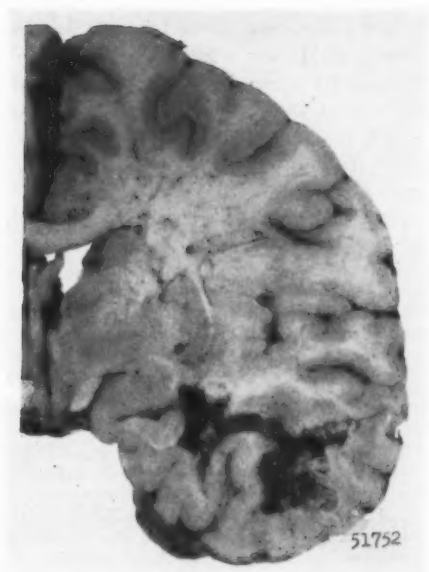
Fig. 5.—51-752D. Enlarged view of abscess showing irregular cavitation of abscess, the thin layer of purulent exudate without capsule formation point of rupture into inferior horn of lateral ventricle also shown.

CASE 5. A sixty-year-old Caucasian man has been under the author's care since 1940. At the age of seven a left incomplete mastoidectomy had been performed. There had been intermittent purulent otorrhea since the onset. He was repeatedly warned of the possibility of developing intracranial complication. He wanted "to wait and see." Five months prior to admission he sustained a basal fracture from a fall in an elevator while at work. There was some bloody discharge in his right ear at the time. He recovered well enough to resume his work until the morning of admission when he suddenly lapsed into coma. Pneumococcus was recovered in his spinal fluid which had a cell count of 2800 per cmm. He eventually recovered from meningitis. Four weeks after admission a left radical mastoidectomy was performed. His postoperative course was uneventful and he was dismissed 43 days after entry.

Experience has shown that the best procedure in these instances is, first, to control the meningitis by administration of adequate and appropriate antibiotics and then later to eliminate the focus of the primary infection in the temporal bone.

Ten patients in this series died within a few hours to six days after admission to the hospital. All these had one common symptom, that

of long years of chronic otitis media and intermittent otalgia and
otorrhea for which they received occasional medical care. All were
in coma and two had bacteremia at the time of their entry. Two were
known to be chronic alcoholics. The third was an insulin-controlled
diabetic. In five patients a pneumococcus was isolated from the spinal
fluid. In another a beta Streptococcus hemolyticus was the invading
organism. In others the organism failed to grow on the usual culture
media. A radical mastoidectomy was performed on four.

CASE 6. A 38-year-old Negro married man was admitted to the hospital in a
stuporous state. He had a life-long history of a chronic draining right ear. Five
days prior to admission there was acute exacerbation of drainage. His temperature
on entry was 104.4° F. A right radical mastoidectomy was then performed. There
was found a large mass of cholesteatoma, thrombosis of the lateral sinus and cerebral
softening. He received massive multiple antibiotics but expired within 24 hours
after entry. Figure 1 indicates the various observations made in this man. It will
be noted that this is one of the rare instances in which thrombosis of the lateral
sinus has developed after administration of antibiotics.

CASE 7. A Caucasian woman, aged 24, had an acute exacerbation of chronic
mastoiditis four months previous and again one week before admission. She had
an inordinate fear of surgical intervention and consistently refused to have any
operative procedure on her ear. On the day of her admission she developed a pro-
gressive elevation of temperature. In the hospital she received multiple antibiotics.
On the third day she experienced several grand mal seizures. A right radical mas-
toidectomy was performed and it was found that the dura was not involved in the
acute inflammatory process. She recovered from shock, but on the sixth day sud-
denly developed respiratory embarrassment and expired. The immediate cause of her
death was pulmonary edema. The meninges were infiltrated with many round cells.
The purulent exudate covered the convolutions in patches at several areas, showing
that the process of healing was actually going on in response to biochemical therapy.

CASE 8. The patient was a 67-year-old Caucasian married man who gave a
history of having had chronic left otorrhea of 30 years' duration. Six months prior
to admission a left modified radical mastoidectomy was performed in another hospital.
There was no apparent effect on his aural discharge after this operation. He com-
plained of increased pain in both eyes on admission. His spinal fluid contained 770
cells per cmm of which 40 per cent were polymorphonuclears. No organism grew
on the usual culture media. He was placed on multiple antibiotics and sulfa drugs.
He expired on the fourth day. Autopsy indicated purulent meningitis, osteomye-
litis of the left temporal bone and subdural abscess.

In Case 7, the antibiotic therapy partially cleared the meninges
from infection; but the patient died of overwhelming toxemia and
pulmonary edema.

In Case 8, osteomyelitis of the temporal bone persisted after the
original mastoidectomy and the patient developed a subdural abscess
from bony erosion. The failure of the response to chemotherapy may
be accounted for in part by the presence of organisms not susceptible
to this drug. The delay in recognition of petrositis may be attributed

in part to masked symptoms. The rational approach should have been the eradication of the focus by a revision of the mastoid before the development of the subdural abscess.

It is time we realized that no antibiotic is a substitute for well performed temporal bone surgery in these instances. Every patient with chronic otorrhea is courting the possible danger of intracranial disaster. Untreated, his hearing progressively deteriorates with each passing year. The otologist has much to offer for those suffering with chronic mastoiditis. A successful tympanoplasty restores much hearing and eliminates infection.[5] A modified radical mastoidectomy helps to preserve the remaining hearing and clears infection. It is too dangerous to perform a cortical mastoidectomy alone in chronic mastoiditis.[4]

Whether to perform a complete radical mastoidectomy, including apicectomy in rare instances, or a modified radical mastoidectomy, or some form of plastic surgery of the middle ear must be determined by the situation encountered. In acute overwhelming infection, the time element plays a vital part. Every defensive force of the host must be marshalled to stem the tide of infection. In contrast with chronic infection, the middle ear can be treated conservatively and hearing is restored to the pre-operative level in most instances.

SUMMARY

Twenty-eight cases of of meningitis in adults observed in a general hospital are presented. Five were associated with acute otitis media. There were two deaths. One of these developed concurrent meningitis due to severe head injury. In the other case, death appeared to be due to a failure of the organism to be controlled by antibiotic therapy in overwhelming acute mastoiditis. The infection occurred either through a retrograde venous spread or contiguous propagation from the primary focus in the temporal bone.

In 23 cases there was a history of chronic suppurative otitis media and chronic mastoiditis. Ten of these died in the institution. In the light of our experience many of these could have been saved had they received adequate medical and surgical therapy before the organisms invaded the intracranial structures.

Those who survived this serious complication required an average of 45 days of hospitalization and suffered corresponding economic loss. No chronic draining ear is safe until the infection is completely

eradicated. Modern surgery of the temporal bone is founded upon safe, sensible, and scientific knowledge and experience. The period of convalescenc from such a surgical procedure is relatively short. There is much to be contributed by the otologist, even in this antibiotic era in the reduction of both morbidity and mortality of acute and chronic otitic infections.

436 SOUTH BOYLE AVE.

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XXIV

PRIMARY QUINSY TONSILLECTOMY

G. H. Bateman, M.A., B.M.

J. Kodicek, M.B.

London, Eng.

Diseases of the throat have been studied and described since the earliest times. Quinsy is a medieval English word describing any throat infection, and especially tonsillitis. It is adopted from the Latin quinancia and both are derived from the Greek cynanche. Before the time of Hippocrates all inflammations of the throat and neck were described by the single term cynanche, but in the Hippocratic writings this term was reserved for internal inflammations,[13] especially those accompanied by difficulty in breathing and swallowing. The original Greek term is derived from a combination of "dog" and "to throttle." The reason for this odd terminology is lost in antiquity but Aretaeus of Cappadocia in the 2nd century A.D. explains the connection between cynanche and cunnus (dog) as "either because it was a common affection of those animals or from its being a customary practice for dogs to protrude their tongue even in health."[1] He then goes on to describe the condition in a special chapter "On the cure of quinsey." Cynanche and quinsy continue to describe tonsillitis until the turn of the 19th century, when quinsy became synonymous with peritonsillar abscess. While the prognosis was always generally good, isolated cases of disastrous complications are reported in the literature over the last three centuries. According to the Registrar-General's returns 226 persons died of quinsy in England in 1875 and the numbers have varied between 623 and 110 between 1848 and 1876.[10]

Incision of what may have been a quinsy is mentioned by Hippocrates (Prognostic, xxiii). The French surgeon, Guy de Chauliac (1300-1367), described incision of the peritonsillar abscess and the method has not been greatly advanced since. Mackenzie (1880) states ". . . as soon as pus has formed, it is better to open the abscess at once than to leave it to evacuate itself spontaneously." He also adds a plea against blood letting, which was still extensively used at the time.

One hundred years ago Chassaignac did not hesitate to perform primary tonsillectomy as a means of draining a peritonsillar abscess. But it was not until about 70 years later that Canuyt was able to confirm the safety and efficiency of the method in a convincing number of cases. Since then a number of surgeons in this country[12,14] and on the Continent[8,9,15] have adopted abscess tonsillectomy as the routine method of treating quinsy. Opinion continued divided concerning the timing of the operation, localization of the abscess, removal of the other tonsil and even the total excision of the affected tonsil.

CLINICAL MATERIAL

Peritonsillar abscess is by no means rare. One hundred and twenty abscess tonsillectomies were performed between December 1949 and February 1958. In addition, a number of other cases were seen which could not be admitted owing to a shortage of beds, and had to be treated by incision and drainage. It is estimated that about 20 cases are seen in the hospital each year. The majority report to the casualty department and would be treated there unless a day and night specialist ear, nose and throat service were available. This may account for the small number of quinsies seen by some laryngologists attending a number of widely distributed hospitals.[11] The incidence as related to the season of the year caused some surprise, as the admissions were evenly spread through the summer and winter months. There was only a slight but probably not significant rise in the spring and autumn. A similarly even incidence was noted by Morell Mackenzie in 1880, but presumably his explanation that patients are less likely to venture forth to hospital during the inclement seasons is not applicable to London in the second half of the 20th century.

Quinsy is a disease of young adults. The age incidence ranged from 5 to 69 years, being highest in the third decade. Over three-quarters of the cases were 10 to 39 years old (Table I).

TABLE I

Age	0 - 9	10 - 19	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69
Number	4	28	39	25	19	4	1

Sixty-five of our patients were males, thus giving a slight preponderance of 54% to men in the series.

Five patients gave a history of tonsillectomy in childhood. Thirty-seven had one or several attacks of peritonsillar abscess and

a further 34 had repeated tonsillitis in the past. Thus 59% of the cases had previous tonsillar infection, while 37% were free from any throat disease in the past. The past history was not commented on in the remaining 4% of cases.

Eighty-four cases (70%) had received no treatment when first seen in hospital. This is not surprising, as the majority of our cases sought medical attention in the Casualty Department without first consulting their own family doctor. (A large number were otherwise fit young Irishmen who had only recently joined the local industrial casual labor force and had not registered with a practitioner in the district.) It is significant, however, that 30% of our cases required operation in spite of having received chemotherapy before admission (penicillin as a rule) and in two cases incision was not successful in draining the abscess.

In the 120 patients the quinsy was right-sided in 58, left-sided in 49 and bilateral in 13. Marked trismus was present in two thirds of the cases (79) and respiratory distress in three. Severe dysphagia and pain was a constant symptoms in all the cases. One patient had pulmonary tuberculosis controlled with an artificial pneumothorax, and one was three months pregnant at the time of operation. Both continued to make normal progress after operation.

THE OPERATION

Endotracheal anesthesia is required. It is essential to obtain the services of a skilled anesthetist who appreciates the difficulties which may be encountered during induction. In some cases the peritonsillar edema spreads along the glosso-epiglottic and aryepiglottic folds towards the larynx. The glottis in these patients is kept patent by the laryngeal abductors, and if the tone in these muscles is abolished by a relaxant the airway becomes occluded by the neighboring edematous folds. As a result the now apneic patient cannot be inflated with oxygen and intubation becomes difficult or impossible. An old-fashioned inhalation induction of anesthesia is therefore recommended with the patient tilted in the head down position. The nasotracheal tube is passed while the patient is still breathing spontaneously. An electric sucker is always readily available for the anesthetist. Thus if any infective material should escape from the quinsy it will tend to flow into the nasopharynx and can be aspirated from there, and the risk of inhalation is minimized.

One hour before operation an injection of 500,000 units of crystalline penicillin is given together with the usual pre-operative

drugs (omnopon and scopolamine). The operation itself is carried out in the same way as an interval tonsillectomy. The peritonsillar abscess separates a large part of the tonsil from its bed, making its enucleation easy. The other tonsil tends to bleed more than average but this bleeding is usually controlled without undue difficulty.

After operation the patient is treated in the same way as any other case after tonsillectomy and in addition receives a daily injection of a long-acting penicillin preparation for five days. Convalescence was typically uneventful. Pain was not a striking feature and many patients spontaneously commented that it was less than before operation. Three cases of secondary hemorrhage were encountered and all settled with conservative treatment. Only one had to be readmitted for a few days. In two cases the bleeding was from the tonsillar bed opposite the quinsy. No postoperative chest complications were seen in any of the cases. Septicemia, which is held up by some as a possible danger, was not met with.

One fatality was reported in a previous paper.[2] This was in a man already dying of a mediastinal extension of the abscess and occurred in spite of immediate drainage of his parapharyngeal, cervical and mediastinal abscesses rather than because of it. It is regarded as an argument in favor of early abscess tonsillectomy in order to prevent such complications.

The average stay in hospital was seven days. Incision and drainage of a peritonsillar abscess and routine tonsillectomy each require a similar period in hospital or at home.[2] Quinsy tonsillectomy, therefore, offers an economic advantage in shortening the period of disability by at least a half. In addition it provides a safe and reliable one-stage method of curing peritonsillar abscess.

COMMENT

Wide incision and dependent drainage are the basic principles governing the treatment of abscesses anywhere in the body. Abscess tonsillectomy fulfills them very adequately, as the entire medial wall of the abscess is removed. In addition no definitive second operation is required after the abscess has been drained. Quinsy tonsillectomy has revealed many varieties of peritonsillar abscess. While the majority present at the upper pole of the tonsil, many originate much lower down, often posteriorly. Some are multilocular and a few extend laterally into the parapharyngeal tissues and even into the deep fascial spaces of the neck. Study of Table II shows that while half the

TABLE II

SITE OF ABSCESS	UPPER POLE ANTR.	UPPER POLE POSTR.	WHOLE TONSIL	CEN- TRAL	LOW POSTE- RIOR	MULTI- LOCU- LAR	ENCYS- TED	CELLU- LITIS	NOT STATED	TOTAL
Number	50	11	6	12	13	7	3	4	27	133
Per Cent	37.6	8.3	4.5	9.0	9.7	5.3	2.3	3.0	20.3	100%

abscesses presented at the upper pole, eleven of them were placed posteriorly and thus deeply. Thus only 41% could have been incised with any certainty. Even assuming that all those abscesses, the site of which was not stated, were probably presenting anteriorly at the upper pole, the percentage of easily accessible quinsies would only be 47. Thus incision in rather over a half the patients would probably have failed to locate the pus. At best, incision might have been put off for a day or two while the pain, trismus and dysphagia continued to increase. Nor is such a period of waiting for the quinsy to point free from risk, as the pointing may be laterally into the neck or even inferiorly towards the larynx. When the time is ripe and successful incision is performed, immediate relief of pain follows. This is not, however, synonymous with the immediate emptying of the abscess. Drainage is in an up-hill direction and residual pockets of infection may result in repeated flares of quinsy, extension into the parapharyngeal tissues or the establishment of an encysted chronic abscess. It is submitted that simple incision of a quinsy is not simple because of the trismus and the inconstant situation of the abscess. It results in poor drainage and finally a second operation of tonsillectomy is required after an interval of 3 to 6 weeks. If the next opportunity for admission is delayed much beyond this optimum period the tonsil becomes virtually cemented into its bed by tough scar tissue, making dissection technically difficult.

Abscess tonsillectomy has the advantage of being a one-stage curative procedure. The operation is technically easy and is followed by a relatively painless and uncomplicated convalescence. The presence of complications is regarded as an indication for urgent abscess tonsillectomy which provides for simultaneous drainage of the quinsy and all its extensions. Its performance in the earlier stages of peritonsillar abscess effectively prevents any extension or reactivation of the infection. Immediate abscess tonsillectomy has proved to be a safe and reliable method of treating peritonsillar abscess while also being the most economical of the patient's and the hospital's time.

The one essential safeguard to this operation is the availability of highly skilled anesthetic assistance. Without this the operation should not be attempted.

SUMMARY

1. One hundred and twenty patients with peritonsillar abscess were treated by primary abscess tonsillectomy.

2. With modern surgical and anesthetic facilities it is regarded as the treatment of choice.

3. The operation offers no special technical surgical difficulties and postoperative complications are rare.

4. A second operation for interval tonsillectomy is avoided.

5. Incision and drainage is regarded as only a second best line of treatment where the essential facilities are not available.

55 HARLEY ST.

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XXV

THE EFFECTS OF CATIONS
ON
LABYRINTHINE ACTIVITY

Yasushi Koide, Ph.D., M.D.

Kokichi Seki, M.D.

AND

Masanori Morimoto, M.D.

Niigata-Shi, Japan

It is well known that potassium ions play an important role in delineating the functions of cations in the animal labyrinth and elicit the characteristic responses when administered intracochlearly.

In 1952, Tasaki and Fernandez[1] reported an experiment on the guinea pig wherein the effects of potassium ions upon the electrical response of the cochlea were studied. Davis and his associates[2] reported a similar experiment. These investigators showed that injection of small quantities of artificial endolymph (high K, low Na) into the scala media had little or no effect upon the electrical sign of cochlear activity, and artificial perilymph containing sodium and potassium in the usual tissue-fluid ratio (high Na, low K) was toxic. Shimamoto[3] reported that perfusing the endolymphatic sac of the guinea pig with potassium chloride solutions evoked spontaneous nysstagmus, and that the group of animals given larger injections of calcium chloride, magnesium chloride, atropin, adrenalin, glucose, and streptomycine, instead of potassium chloride into the endolymphatic sac, had no vestibular reaction. Furthermore, he claimed that the disturbance of potassium metabolism of endolymph may result in hyper- or hypofunction of the vestibule, and that he established the physiological dependence of Ménière's disease upon the potassium level of endolymph.

These recent experiments indicate that the labyrinthine activity may be significantly varied by small changes in the potassium and

sodium pattern of endo- and perilymph surrounding the labyrinthine tissues.

Although Shimamoto[3] reported that magnesium and calcium ions do not exert their effects on the labyrinthine activity, there is no clear-cut evidence available which would not implicate these ions in the chain of events by which cations exert their effect on the labyrinth, since larger injections and complete perfusions of the scala media are complicated by probable mechanical injury.

From the biochemical point of view, in all body fluids relatively constant amounts of cations and anions must be maintained by the cell for it to function normally.[4,5] Since any disturbance in the ratio of ionic species in the tissue may stimulate profound changes, followed by changes of entropy production, a consideration of ionic effects on the labyrinthine activity in terms of the energy producing system would be of considerable value.

EFFECTS OF CATIONS ON VESTIBULAR REACTION

Previous authors have shown that vestibular reaction may be induced by unilateral stimulation or ablation of the vestibule. Vestibular reaction may also be produced by unilateral intratympanic injection of salt solutions[6] as well as by injections of metabolic inhibitors[6,7] into the tympanic bulla. This finding opened the possibility to determine 1) the ionic effect on labyrinthine activity and 2) the relationship between the species of metabolic inhibitor or stimulant, the level of enzymatic activity, and the production of labyrinthine disturbance.

The vestibule was selected for the present study because of the comparatively simple experimental procedure of its function without injurious effect on the labyrinth itself.

In all experiments, animals without any evidence of a disturbance in vestibular reaction were studied. Salt solutions were administered into the left tympanic bulla of adult rabbits by means of a syringe, and isotonic sodium chloride solutions into the right tympanic bulla. In such cases, the volume was about 0.3 to 0.6 ml. Control was obtained by intratympanic injections of isotonic sodium chloride solutions into both ears. Guinea pigs weighing 400 to 600 g were also used for the same study.

As shown in Table I and Figure 1, vestibular reaction was demonstrated in many animals, using sodium chloride, potassium chloride,

TABLE I

THE EFFECTS OF ELECTROLYTES ON VESTIBULAR REACTION

ANIMAL	ELECTROLYTE		TOTAL CASES	CASES WITH INDUCED SPONT. NYST.	CASES WITH FALLING TO LEFT SIDE, ACCOMPANIED BY SPONT. NYST.
		Control	10	0	0
		NaCl	7	0	0
	Hypertonic	KCl	6	3	3
	solution	CaCl₂	10	9	9
Rabbit		MgCl₂	9	0	0
		KCl	10	0	0
	Isotonic	CaCl₂	14	7	1
	solution	MgCl₂	7	0	0
		Control	10	0	0
		NaCl	8	1	0
Guinea pig	Hypertonic	KCl	4	3	3
	solution	CaCl₂	6	6	6
		MgCl₂	6	2	0

calcium chloride and magnesium chloride as an electrolyte. The present results indicate that calcium chloride was a more effective electrolyte than potassium chloride, although both were effective. In contrast, sodium chloride and magnesium chloride were rather poor. The changes of vestibular activity influenced with the above electrolytes are those expected to result from hypofunction of the vestibule: spontaneous nystagmus toward the right side, falling to the left side and ataxia.

In the course of the present study, it seems desirable to ascertain whether the observed vestibular reaction was attributable to the toxic effect of cations or to the change of osmotic pressure of the perilymph. Then, after three hours of intratympanic injections of salt solutions, perilymph for chloride analysis from both ears was collected by piercing the oval window membrane with a dry glass capillary. The chloride was titrated with silver nitrate in a perilymph made fairly acid with sulfuric acid by the method of Cunningham, Kirk and Brooks.[8] The end-point was determined potentiometrically by use of a silver-silver amalgam electrode pair operating as a bimetallic system. Protein need not be removed if the acidity of the medium is adjusted properly to avoid formation and coprecipitation of silver protein compounds.

TABLE II

CHLORIDE CONTENT OF PERILYMPH AFTER INTRATYMPANIC INJECTIONS OF THE SALT SOLUTIONS

SOLUTION		CHLORIDE CONTENT (mg/dl)	
RIGHT	LEFT	RIGHT	LEFT
		402	545
Isotonic	Isotonc	392	437
NaCl	NaCl	441	402
		414	402
		402	472
		478	472
Isotonic	Isotonic	414	385
NaCl	KCl	372	351
		472	497
		567	497
		392	472
		459	441
		426	414
Isotonic	Isotonic	459	426
NaCl	CaCl₂	459	402
		472	472
		441	459
		472	484
		509	459
		362	362
Isotonic	Isotonic	441	441
NaCl	MgCl₂	414	437
		472	426
		441	484

The results of these analyses of perilymph are given in Table II. From an inspection of this result, it is suggested that the observed vestibular reaction evoked by the salt solutions was probably a true toxic effect of cations.

SUCCINIC DEHYDROGENASE ACTIVITY OF THE LABYRINTH AND VESTIBULAR REACTION

Some years ago dehydrogenase activity was demonstrated in the cochlea of the guinea pig using succinate as substrate.[9-12] This observation provides some suggestion for the presence of the tricarboxylic acid cycle in the cochlea.
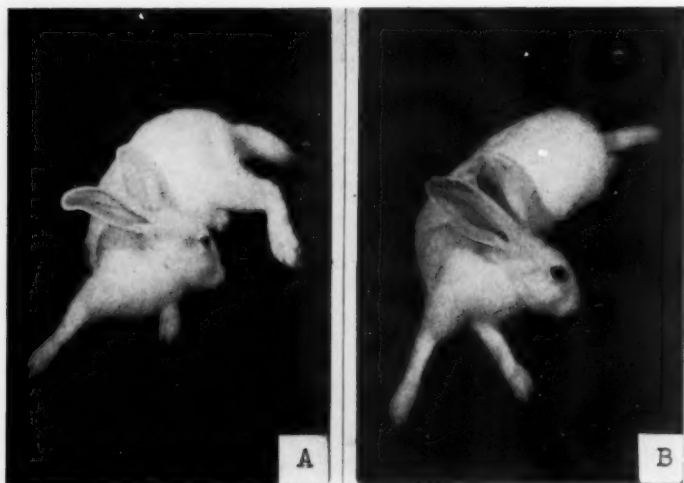
Fig. 1.—Vestibular reaction elicited by intratympanic injections of salt
solutions into the left ear.   A: A rabbit treated with 10 per cent calcium
chloride solution.   B: A rabbit treated with 10 per cent potassium chloride
solution.

It must be assumed that metabolic energy is used for the process
in the vestibular reaction.   Hence, it is not surprising to find evidence
for the active metabolism of certain compounds involved in the tri-
carboxylic acid cycle and for the activity of electron transport sys-
tem.   According to Koide and Imokawa,[7] the localized regions in the
labyrinth, i.e., the organ of Corti, stria vascularis, limbus spiralis,
spiral ligament of the cochlea, and the hair cells of the vestibule, gave
indication of high activity of the electron transport between reduced
diphosphopyridine nucleotide or succinate and molecular oxygen by
way of the cytochrome system.

Since little is known about the metabolic activity of the labyrinth
with hypofunction, the present study is concerned with the vulnera-
bility of histochemically demonstrable succinic dehydrogenase in the
labyrinth during its discordant phase after intratympanic injections
of calcium chloride and potassium chloride.

Guinea pigs weighing 400 to 500 g were killed by cutting the
common carotid artery, when the animals demonstrated spontaneous
nystagmus after injections of the salt solutions.   The bony labyrinths

were removed from that side the salt solutions were given, and were washed briefly in saline to remove any blood.   Then the bony labyrinths were divided by a knife in two portions, i.e., the bony cochlea and vestibule, and several holes were drilled through the bony capsule of each portion with a dental burr to facilitate rapid infiltration of substrate into the inside of the labyrinth.   Such labyrinths were incubated with neotetrazolium-succinate reagent in phosphate buffer at 37° C.   These preparations were fixed in formalin after two hours of incubation.   The membranous tissues were removed from the bony capsule and embedded in gelation; sections were cut at 20 μ and then mounted on the slide glass.

No significant variation in degree of intensity of staining, depending on the electrolytes, are shown in Figure 2, although marked vesibular reaction was observed in each animal.   This experiment on succinic dehydrogenase has not implicated this enzyme as a major sign of labyrinthine activity, in agreement with Koide[6] and Koide and Imokawa.[7]   In the manometric studies[13] on the metabolism of the labyrinth, the activity of enzymes involved in the tricarboxylic acid cycle was measured, and it became clear that succinic oxidase is highly resistant to anoxia while the other enzymes are rather vulnerable.

This observation suggests that, in abnormal condition, the change of the tricarboxylic acid cycle may not be preceded by change of activity of succinic oxidase, but that of the other enzymes.

EFFECT OF CATIONS ON THE OXYGEN TENSION
IN THE LABYRINTH

The experiments in the previous chapter failed to demonstrate the inhibition of vestibular activity, resulted from the injection of salt solutions, incidental to inhibition of succinic dehydrogenase activity.   The possible participation of cations in the hypofunction of the labyrinth might, however, be approached from another angle.   For instance, we may study experimentally whether the injection of salt solutions has any effect on oxygen tension in the labyrinth.   Hence, the examination had to be restricted mainly to such cations as have a marked inhibiting effect on the labyrinthine activity.   The cations employed for this purpose were calcium chloride and potassium chloride, and sodium chloride was used as a control.

Rabbits were narcotized by the intraperitoneal injection of sodium barbiturate, supplemented with curare.   The animals were first tracheotomized and artificial respiration was used in all these experiments.   The bulla was dissected and opened and the labyrinth

Fig. 2.—Histochemical demonstration of succinic dehydrogenase activity in the vestibule (crista ampullaris) of guinea pig with induced vestibular reaction, resulted from intratympanic injections of salt solutions. A: Control. B: 10 per cent potassium chloride solutions. C: 10 per cent calcium chloride solutions. There is no significant variation of the enzymatic activity between animals. Same result has been obtained from the same enzymatic observation on the cochlea of guinea pig.

was exposed. The operative approach, insertion of platinum micro-electrode in the basal turn of the cochlea and fixation of AgCl electrode in the vestibule, have already been described.[14] In recording the change of oxygen tension, these electrodes are placed in the circuit of an oxigraph.

One ml of hypertonic solutions of these cations was infused into the tympanic bulla on the side on which the labyrinth was exposed. The change of oxygen tension was recorded by means of an oxigraph at frequent intervals, usually every five minutes.

In the control experiment, a rabbit was given 1 ml of 10 per cent sodium chloride solution intratympanically. The injection produced, after a certain interval, a rapid rise of the oxygen tension followed by a rapid fall to normal level. Then, after 30 minutes, the oxygen tension dropped to a lower level, as shown in Figure 3A.

Figure 3B represents a rabbit that was given 10 per cent potassium chloride solution. Immediately after injection, the oxygen tension fell steadily, and then, after two hours, recovered to normal level. At the end of the experiment, the oxygen tension rose markedly.

Figure 3C represents a rabbit that was given 10 per cent calcium chloride. The shift of oxygen tension was identical with that given in Figure 5B, except that it leveled off more markedly than the latter.

The oxigraphic (i.e., polarographic) procedures using solid microelectrodes to determine the oxygen content of electrolyte solutions and of various tissues, such as brain and skin, have found application in many biological problems. Use of the electrodes *in vivo* may be influenced by movement of the tissue, the rate of oxygen diffusion through the tissue, ischemia produced by pressure of the electrode, and the presence of red cells on the platinum surface. However, the best results would, of course, be obtained if in the practice of such method the current was conducted from the large and simple organ such as major blood vessels and the chamber of the heart. Clark et al.[15] recorded successfully the change of oxygen tension in the aorta for three hours. On the other hand, recording of oxygen tension in the labyrinth presents many difficulties, because of the fine structure in the labyrinth.

When the holes are drilled through the bony capsule of the labyrinth, the perilymph may possibly leak out through the slits between the bony wall of the holes and the electrodes, even if the elec-
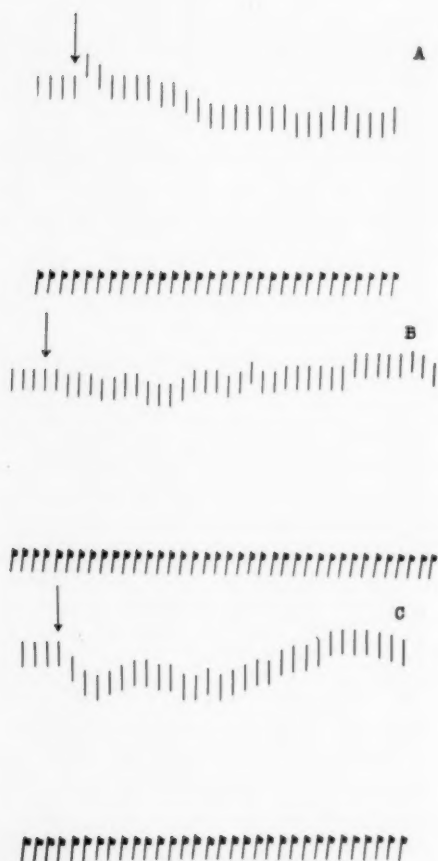
Fig. 3.—The cationic effects on the oxygen tension in the labyrinth.
A: 10 per cent sodium chloride solution. B: 10 per cent potassium chloride
solutions. C: 10 per cent calcium chloride solutions. Time trace: five min-
utes. Arrows indicate when the salt solutions were infused.

trode just fits the holes. Furthermore, the electrode should preferably
be inserted into the perilymphatic space, but under certain circum-
stances this is impossible without injury to the fine structure in the
labyrinth. It seems reasonable to assume that if the experiment is
prolonged, these factors will significantly affect the condition of the
labyrinth or, in other words, the labyrinth will become fatigued,
probably followed by the decline of oxygen tension in the labyrinth.

Fig. 4.—The shift of the oxygen tension in the labyrinth, caused probably by any operative failure, before infusion of salt solutions. Time trace: five minutes.

Then, for the purpose of obtaining a reliable result, the observation must be carried out in the earlier period of the experiment (according to our experiences, within 30 minutes).

In one animal, represented in Figure 4, an exponential decline of the oxygen tension in the labyrinth was obtained before infusion of the salt solutions was introduced, and the curve closely resembles that observed in the cutting experiment on the labyrinthine artery,[16] except that it declines even more slowly. It is conceivable that this phenomenon is related to the analogous one in the labyrinth impaired by any operative failure. Thereby, the physiological lesion in the labyrinth caused by any failure is the blocking of oxygen supply which gives rise to decrease in oxygen tension in the labyrinth.

To sum up, it is concluded that each shift of the oxygen tension shown in Figure 3 was not caused directly by any operative failure, but by the true toxic effect of calcium and potassium ions.

COMMENT

In the problem of the chemical physiology of the labyrinth, there may be several mechanisms linking metabolism to bioelectric effects. One is the accumulative process, which concentrates such an ion as potassium in endolymph. According to Smith et al.[17] the endolymph of the guinea pig was found to have a potassium concentration 30 times that of perilymph, and a sodium concentration only one-

tenth as high as perilymph. The maintenance of potassium and sodium ion gradients, consequently, is an essential step in the production of bioelectric potentials in the labyrinth. Much remains to be investigated but it is clearly linked to aerobic metabolism.

Previous authors[1,2] have shown that, when the gradients cease to exist, the biochemical potentials in the cochlea run down and disappear. In same manner, depression of biochemical potentials in the vestibule must occur on exposure to alteration in the gradients, followed by hypofunction of the vestibule, because, in general, a dead cell has a low potential difference and fails to respond to ionic substitutions. But there are other effects (of oxygen tension,[18-23] poisons,[2,6] hypoglycemia,[6] etc.) that may occur so quickly that alterations in gradients may hardly be fast enough to account for the changes observed. Many of these rapid changes may be due to alteration of the surfaces across which the gradients set up potentials. The surfaces are themselves the products of metabolism, and may remain subject to metabolic influences.

From the biochemical point of view, potassium ions have stimulatory effects.[4] For example, potassium ions enhance glycolysis. Thus, yeast fermentation is more vigorous in the presence of 0.01 M potassium ions, but sodium ions are far less effective. Potassium ions in 0.0025 M concentration increase tumor glycolysis, whereas sodium ions are inhibitory. According to Ashford and Dixon,[24] Dickens and Greville,[25] and Dixon,[2] potassium ions cause pronounced effects on the metabolism of glucose by slices of cerebral cortex, increasing aerobic glycolysis and respiration.

On the other hand, calcium ions[5] inhibit oxidative phosphorylation without inhibiting oxidation. Phosphrylations[27] involving adenosinetriphosphate usually require magnesium for full activity. Some of these are inhibited by calcium or sodium ions, pyruvatephosphoferase, for example. Others are not inhibited by calcium, such as creatine phosphoferase and some are activated by either magnesium or calcium, adenosinetriphosphatase, for instance.

This fact suggests that several steps in the phosphate transfer system which make oxidative energy available for maintenance of structure and function of cell are sensitive to calcium ion concentration.

From the neurophysiological point of view, each of the potassium and sodium ions has been assigned at least one special role in neural

processes. They are the principal current carriers in the membrane and their exchange accounts for the action current. In contrast, calcium ions react with and become part of the surface of the cell.

The physiological properties of the cations have been compared with this background. In the present study by the intratympanic injection method, the cations, especially calcium and potassium ions, appeared to inhibit the function of the labyrinth in the direction: calcium > potassium > sodium and magnesium. Moreover, the inhibitory effects of the cations on the oxygen supply to the labyrinth were well-demonstrated and its effects appeared to rise in the order: sodium < potassium < calcium.

The calcium effect at first is interpreted as due to the inhibition of metabolism of the labyrinthine tissues, the structure and function of which are sensitive to calcium ions. We further refer to the above-mentioned change of the oxygen tension in the labyrinth which can be thought of as being indicative of the activity of the labyrinth. Then, the change of the oxygen tension may be correlated with the alteration of the labyrinthine tissues.

On the other hand, it is assumed that exposing the perilymphatic raum to a surplus of potassium ions at first releases a rapid potential fall, which is followed by a hypoactivity of the labyrinth persistent during the continued presence of potassium ion, and that the potential fall may cause the depression of the oxygen tension.

CONCLUSIONS

1. Vestibular reaction was demonstrated in many animals, after unilateral intratympanic injections of salt solutions. In this study, the cations, especially calcium and potassium, appeared to inhibit the function of the labyrinth. Moreover, the inhibitory effects of the cations on the oxygen supply to the labyrinth were demonstrated.

2. No significant variation in degree of the activity of succinic dehydrogenase was demonstrated in any animal with marked vestibular reaction evoked by intratympanic injections of salt solutions.

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XXVI

OSTEOMYELITIS OF THE
FRONTAL BONE

HARRY P. SCHENCK, M.D.

PHILADELPHIA, PA.

Although osteomyelitis may involve the bony walls of any of the paranasal sinuses, its appearance elsewhere than about the frontal sinus is a rarity. Involvement of the frontal bone is attended by numerous and overwhelming complications and, when unarrested, there is progressive necrosis of the entire thickness of the bone followed by extradural and intradural abscesses and suppurative meningitis.

Two clinical types are encountered: the acute, fulminating cases in which meningitis and septicemia may appear within 12 to 24 hours after the first symptoms appear, and the more insidious subacute or chronic cases, characterized by cyclic exacerbations during which there is progressive involvement of the calivarium and the formation of abscesses of the scalp.

Because significant changes in the incidence and clinical manifestations of osteomyelitis of the frontal bone have been observed since the introduction of sulfonamide and antibiotic therapy, the hospital records of 56 patients with osteomyelitis of the frontal bone, treated during the three decades, 1929 to 1958, inclusive, were reviewed to evaluate, if possible, the impact of chemotherapy upon the course of this disease.

The incidence and the mortality rates of the two types of osteo-myelitis of the frontal bone during the three decades are shown in Table I.

During the decade 1929-38, there were 23 patients with osteo-myelitis of the frontal bone; of these, 14 had subacute or chronic infection with two deaths (1 cerebral abscess, 1 meningitis), and 9 patients had fulminant infection with 6 deaths (2 suppurative men-ingitis, 2 terminal septicemia, 1 meningo-encephalitis, 1 cerebral ab-scess).

During the decade 1939-48, of 16 patients with osteomyelitis of the frontal bone, 12 had subacute or chronic involvement and 4 had a fulminant form. The sole death (meningo-encephalitis) occurred in the latter group. The variations in clinical course and survival rate during 1939-48 as compared to 1929-38 are largely accounted for by the availability and wide general use of sulfonamide and antibiotic therapy during the later decade.

During the decade 1949-58, 17 patients were encountered with subacute or chronic osteomyelitis and none with the fulminant form. No deaths occurred during this interval. The valuable guidance of sensitivity tests and the prompt use of adequate doses of the appropri-ate chemotherapeutic agents appear to have modified the fulminant forms of osteomyelitis. Although with present methods of therapy, the more slowly progressing infection is the rule, fulminant forms of the infection must still be anticipated in the absence of effective ther-apy or the presence of resistant micro-organisms.

The organisms identified in the cultures taken from pus, abnor-mal soft tissues and bone are shown in Table II. In each decade, the most common etiologic micro-organism was the staphylococcus aureus (24 patients). Next in frequency of occurrence were the hemolytic streptococcus (12 patients), pneumococcus (6 patients), anerobic streptococcus (6 patients) and hemophilus influenzae (1 patient). Positive cultures were obtained in every fulminant case, but no growth was obtained in some cultures from the chronic cases; in the 1949-58 group, no growth was reported in 5 of 17 patients with subacute or chronic infection (29.4 per cent). Since it has become common practice to administer chemotherapeutic agents at the earliest possible

HARRY P. SCHENCK

TABLE I

OSTEOMYELITIS OF THE FRONTAL BONE

	SUBACUTE OR CHRONIC		FULMINANT		(*) DIED	
1929	1		2	(*1)		
1930	2	(*1)	0			
1931	0		2	(*1)		
1932	2		0			
1933	1		2	(*2)		
1934	1		0			
1935	2	(*1)	0			
1936	1		1	(*1)		
1937	2		1	(*1)		
1938	2		3			
Total	14	(*2)	9	(*6)	23	(*8)
Mortality		14.2%		66.6%		
1939	2		1			
1940	1		2	(*1)		
1941	1		0			
1942	1		0			
1943	1		0			
1944	1		0			
1945	2		0			
1946	0		1			
1947	2		0			
1948	1		0			
Total	12		4	(*1)	16	(*1)
Mortality	0			25.0%		
1949	1		0			
1950	1		0			
1951	2		0			
1952	2		0			
1953	1		0			
1954	2		0			
1955	1		0			
1956	2		0			
1957	2		0			
1958	3		0			
Total	17		0		17	
No deaths						

TABLE II

MICRO-ORGANISMS ISOLATED
OSTEOMYELITIS OF THE FRONTAL BONE

	SUBACUTE OR CHRONIC						FULMINANT					
	Staph. aureus	Hem. strep.	Pneumococcus	Anerobic strep.	H. influenzae	No growth	Staph. aureus	Hem. strep.	Pneumococcus	Anerobic strep.	H. influenzae	No growth
1929-38	6	3	2	1	1	1	4	2	1	2	0	0
1939-48	5	3	1	2	0	1	2	1	1	0	0	0
1949-58	7	3	1	1	0	5						
Total	18	9	4	4	1	7	6	3	2	2	0	0

moment, it is increasingly difficult to identify the etiologic micro-
organisms before osteomyelitis can be diagnosed clinically. With
increasing frequency, cultures taken from pus, abnormal soft tissue
and bone are reported to show no growth on culture media.

Of the 56 patients with osteomyelitis of the frontal bone, none
had had preceding fractures of the frontal bone or direct operations
on the frontal sinuses. In the 13 patients with fulminant osteomye-
litis, acute sinusitis alone appeared to initiate the bone infection
although it must be conceded that immunologic and nutritional fac-
tors may have played a role; in 8 of these patients there were signifi-
cant anatomic abnormalities. Of 43 patients with subacute or chronic
osteomyelitis, 22 had had repeated probing of the nasofrontal com-
munication or attempted irrigation of the frontal sinus with a can-
nula. These traumatizing procedures appear to have perpetuated
the sinus infection by producing increased edema and obstruction
and, in some instances, actual stenosis of the tract.

Predisposing factors included the presence of an osteoma in the
frontal bone (7 of 56 patients [12.5 per cent]) and extensive hyper-
plasia of the sinus mucous membrane. The intermittent administra-
tion or inadequate dosage of chemotherapeutic agents appeared to be

responsible for the development of chronic sinus infection and subsequent bone infection in 11 patients.

While fulminant osteomyelitis of the frontal bone was encountered fairly frequently during the decade 1929-38, only one-half as many cases appeared during 1939-48, and none at all during 1949-58. The decreased incidence of the fulminant forms is attributable to the increased availability and more general use of chemotherapeutic agents. Although fewer cases of fulminant osteomyelitis appeared during the decade of 1939-48, and none at all during 1949-58, there was little variation in the incidence of the subacute and chronic forms. These findings reflect the effectiveness of chemotherapy in modifying primary acute frontal sinus infections so that when bone infection follows subacute or chronic osteomyelitis develops rather than the fulminant form.

While the diagnosis continues to rest on the appearance of fluctuant swelling, advancing edema, persistent low-grade septic fever, leukocytosis, pain and malaise, confirmation still depends upon the radiographic appearance of the bone. The introduction of chemotherapy has made it necessary to revise the concepts of the past in regard to osteomyelitic changes in bone as shown by roentgenography.

Roentgenography is indispensable for the determination of the extent and nature of involvement and for the clarification of the anatomy of the region. However, since extensive bone involvement may exist without radiologic changes and confirmatory x-ray evidence is often lacking in the acute stages, negative x-ray evidence must often be discounted in presence of strong clinical evidence. Bone changes can seldom be detected until 4 or 5 days after the onset of osteomyelitis but, in the absence of chemotherapy, radiologic changes can usually be detected 10 to 14 days after onset. With effective chemotherapy, bone changes are appreciably delayed. While all forms of osteomyelitis of the frontal bone are most easily detected in lateral views of the skull rather than in occipitomental views, the diagnosis of osteomyelitis depends upon the demonstration of destruction of the bony trabeculae.

In the past, the typical, moth-eaten appearance, resulting from the loss of sharpness in the bony framework of the diploe as the bony trabeculae became declacified, was regarded as of prime significance

TABLE III

MAJOR COMPLICATIONS
OSTEOMYELITIS OF THE FRONTAL BONE

	SUBACUTE OR CHRONIC		FULMINANT	
1929-38	Cerebral abscess	1*	Meningitis	2*
	Meningitis	1*	Terminal septicemia	2*
	Orbital abscess	1	Cerebral abscess	1*
			Meningoencephalitis	1*
			Subdural abscess	1
1939-48	Epidural abscess	1	Meningitis	2
	Orbital abscess	1	Meningoencephalitis	1*
1949-58	Epidural abscess	1		

* Death

although it was recognized that swelling of the overlying soft tissues occasionally simulated this appearance. Since the introduction of chemotherapy, the diagnosis of osteomyelitis of the frontal bone continues to depend upon the detection of this destruction of the bony trabeculae but instead of the true, moth-eaten appearance of the past, only slight deossification can be demonstrated in the roentgenograms. An experienced roentgenologist should, therefore, be responsible for the interpretation of the films.

With or without chemotherapy, the most useful radiologic signs in the early stages are decalcification and a loss of the normal pencil-like outline of the sinus wall. With chronicity, alternate areas of decalcification and sclerosis appear, and at this stage, radiology is capable of visualizing the extent of bone involvement and of detecting sequestra. Tomography is extremely valuable in further determining the extent of the osteomyelitic process.

In Table III, the major complications are listed by decades. Fewer complications have been the rule since 1939.

The otolaryngologist bears a heavy responsibility for the prevention of osteomyelitis of the frontal bone. It is not enough to merely control a single, initial attack of acute frontal sinus infection. Recurrences must be minimized by careful consideration of immunologic factors and by the elimination of any anatomic factors responsi-

ble for the vulnerability of the sinus. The blind use of sulfonamide or antibiotic drugs may be condoned at the onset of an overwhelming infection when information concerning the results of sensitivity tests is not as yet available but the subsequent therapy should be based upon the results of sensitivity tests and continued until the infection is completely eradicated. In many instances, chronic sinusitis appears to be the direct result of inadequate and intermittent administration of chemotherapeutic agents during recurrent acute infections of the frontal sinus.

Equally important is the matter of drainage. When pus under pressure produces severe pain, the frontal sinus should be drained without delay; the insertion of a metal or plastic tube, under local anesthesia, is usually adequate. The tube should be permitted to remain in position until vasoconstrictor solutions introduced into the tube escape freely into the nasal chamber or until other means are employed to effect surgical drainage. The introduction of probes and cannulae into the nasofrontal communication frequently results in stricture of the passage, perpetuation of the sinus infection and the eventual extension of infection to bone.

During the decade 1949-58, there has been an impressive decrease in the incidence of the fulminant form of osteomyelitis of the frontal bone due to the effectiveness of chemotherapy in the control of the majority of acute infections of the frontal sinus. Advances in chemotherapy, however, have not eliminated all extension of infection from the frontal sinus to the bony structures about it; insidious, chronic osteomyelitic infections continue to occur with the constant threat of subperiosteal abscess, draining fistulous tracts, meningitis and brain abscess. Moreover, intracranial infection may still complicate acute frontal sinusitis before actual empyema of the sinus has had time to develop.

During the preantibiotic era, when wide removal of diseased bone was imperative because of the lack of known controls against the spread of infection, the operations of Riedel, Killian, Lothrop, Lynch and Kuhnt were life-saving measures. Now they are often no more effective than simple drainage combined with chemotherapy and result in cosmetic deformities unacceptable to both surgeon and patient.

Although the antibiotic drugs exhibit a peculiar ability to relieve the pain associated with osteomyelitis, their main value lies in the

prevention of sequestration and in the arrest of progressive extension of infection to contiguous osseous tissue. Their timely use in osteomyelitis secondary to sinus infections has not eliminated the need for surgical drainage but has reduced the extent of the surgery required for this purpose. Immediate sequestrectomy has been mandatory in the past but the advent of chemotherapy provides strong evidence that osteomyelitic sequestra, instead of becoming detached and cast off from living bone, remain in situ, and become progressively revascularized and reconstituted. By the rapid sterilization of pus and its subsequent absorption or aspiration, the way is opened for "creeping substitution" of the sequestrum.

Since 1949, 17 patients with osteomyelitis of the frontal bone, secondary to suppurative frontal sinus disease, were treated with antibiotic drugs and provided with a simple, permanent drainage tract between the sinus and the nasal chamber. Complete recovery occurred in all 17 patients without further surgical intervention although in one patient the drainage tube required replacement because of obstruction with fibrinous material.

The technique for obtaining permanent drainage of the frontal sinus has been described.[1] Access to the anterior wall of the frontal sinus is provided by an incision in the midline of the eyebrow at its mesial end. The anterior wall of the frontal sinus is penetrated by means of a burr, gouge or chisel, and the opening enlarged only enough to permit the removal of all diseased tissue within the sinus and the exploration of the posterior wall of the sinus. Standard antrum rasps remove the obstructive soft tissue and bone in the nasofrontal channel, break down the walls of the contiguous ethmoidal cell walls which are usually also infected and provide sufficient space for the introduction of a plastic tube not less than 10 mm in diameter. The tube is placed so it fits loosely in the frontal sinus and extending through the prepared channel reaches the nasal vestibule. The external incision is immediately closed after careful approximation of the periosteum and the tube is permitted to remain in place for six weeks; during this time adequate drainage from the sinus is provided while complete epithelialization of the revised tract occurs. At the end of six weeks, the tube is simply withdrawn from the nose.

In one of the 17 patients, a large subperiosteal abscess was drained successfully by this approach. In two of the 17 patients, the roent-

genograms showed bone absorption in the frontal bone as far posteriorly as the coronal suture. In three patients, sequestra were present but not removed; these eventually disappeared. At monthly intervals, roentgen examination was used to determine the postoperative changes in the frontal bone. Two months after operation, the zone of osteomyelitic reaction could no longer be delineated in the films and there was no evidence of reactivation of the inflammatory process. After five months, bone defects and radiolucent areas appeared smaller and, if sequestra were present, they were now smaller but could still be located. Eleven months after operation, sequestra could no longer be identified, and at the end of a year all radiolucent areas had disappeared.

Radiographic studies should not only precede combined antibiotic and surgical therapy, but also be continued throughout the course of the disease until complete recovery is demonstrated. Such periodic observations are of the utmost importance because it is unlikely that all subacute and chronic infections of the frontal bone can be arrested by conservative measures. Moreover, more fulminant forms of osteomyelitis of the frontal bone are to be anticipated because of the recent increased incidence of staphylococcal infections, resistant to chemotherapeutic agents, in other areas.

CONCLUSIONS

1. The use of chemotherapeutic agents has altered the clinical course of osteomyelitis of the frontal bone and reduced the incidence of the more formidable complications.

2. In 17 patients with subacute or chronic osteomyelitis of the frontal bone, the removal of diseased soft tissues, continuous drainage of the frontal sinus and chemotherapy obviated the necessity for radical and obliterative surgical procedures.

3. Periodic radiographic examination is imperative not only to determine the status of the osteomyelitic process but also to assess the effectiveness of the various surgical procedures in current use.

4. It must be anticipated that radical surgical intervention will be necessary in exceptional instances of osteomyelitis of the frontal

bone and especially since the appearance of bacterial strains resistant to chemotherapeutic agents.

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XXVII

AN EXTRALARYNGEAL APPROACH
FOR CERTAIN BENIGN LESIONS
OF THE LARYNX

LeRoy A. Schall, M.D.

Boston, Mass.

Slow growing submucosal supraglottic and intraglottic new growths and cysts of the larynx will eventually, by their encroachment on the airway, require surgical intervention. On indirect laryngoscopy, these growths or cysts appear as a smooth submucosal growth, involving one side of the larynx, obliterating the aryepiglottic fold, bulging over the lumen of the larynx and hiding a view of the true vocal cord.

The laminagram of the larynx will clearly show the tumor mass and will easily differentiate a new growth from a laryngocele, but will not differentiate a new growth from a laryngeal cyst. Direct laryngoscopy will confirm the findings of the indirect examination and the attempt to secure a biopsy is, oft times, followed by profuse hemorrhage and an unsatisfactory biopsy.

During the past year I have had four patients that presented this problem, and I found the solution by an extralaryngeal approach that does not traumatize the endolarynx and that does not have any endolaryngeal complications.

OPERATION

Step 1. If the patient is dyspnoeic, a low tracheotomy is performed under local anesthesia. If the patient is not dyspnoeic, and an intratracheal tube can be introduced, the tracheotomy may be done at the end of the operation. The operation after the tracheotomy may
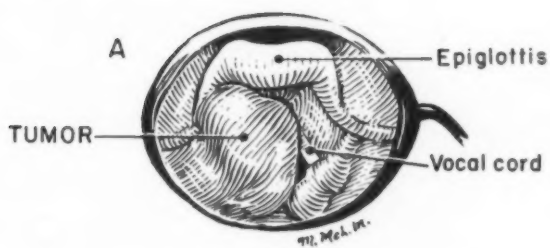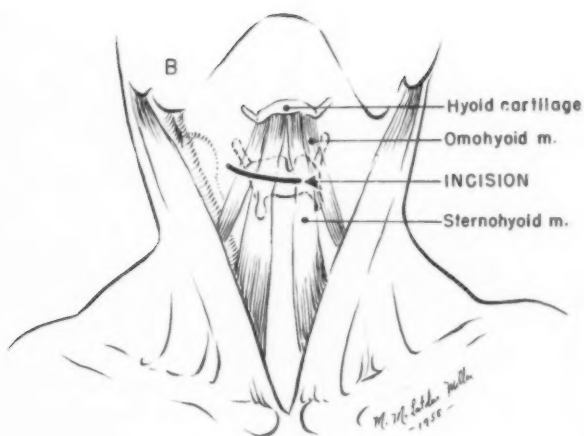
Figure 1

Figure 2

Figure 3

Figure 4

G

Undermining

Thyroid cartilage
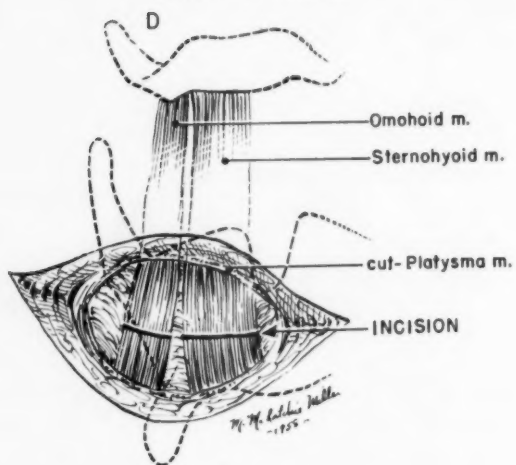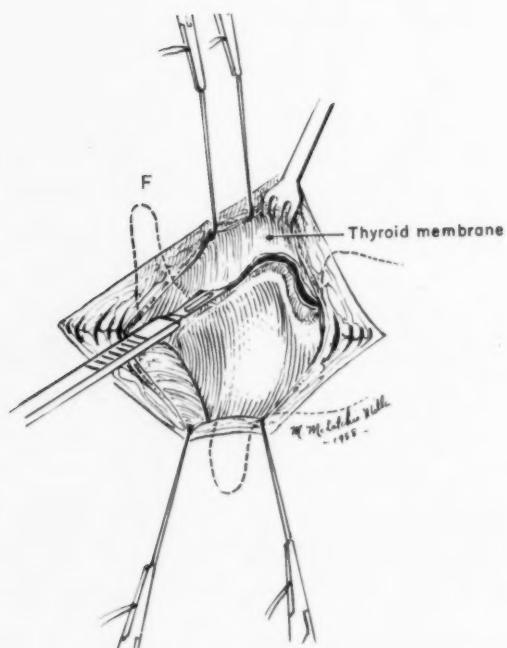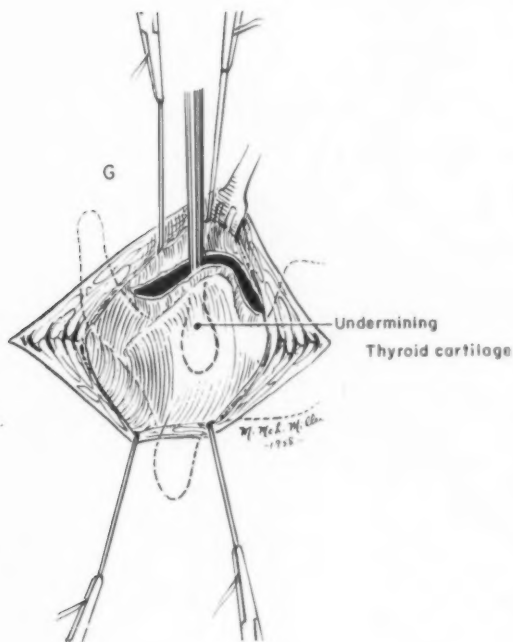
Figure 5

be performed under local anesthesia by infiltration or by cervical nerve block, or under a general anesthesia of the surgeon's choice.

Step 2.   A crease line incision at the upper margin of the thyroid alae from the midline of the neck, laterally for at least three or four centimeters through skin, subcutaneous fascia and platysma muscle, avoiding the superior laryngeal vessels and nerve.

Step 3.   The sternohyoid muscle is identified, isolated, tied between two catgut ligatures and sectioned.   The catgut ligatures are left long and serve as retractors.   The anterior belly of the omohyoid is likewise isolated, tied and cut.   The fibers of the thyrohyoid muscle are cut and wiped off the alae of the thyroid cartilage.
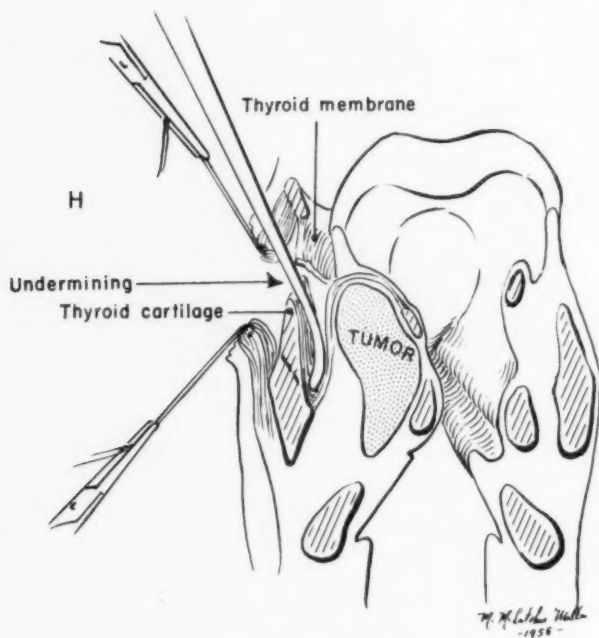
H

Thyroid membrane

Undermining

Thyroid cartilage

TUMOR

Figure 6

Step 4. With the alae of the thyroid cartilage exposed an incision is made along the upper margin of the cartilage through the peri-chondrium.

Step 5. With any blunt elevator, the perichondrium is separated from the inner surface of the thyroid ala.

Step 6. With a biting forceps, the ala of the thyroid cartilage is removed from the midline to the oblique line and from the superior margin down to include at least two-thirds of the cartilage.

Step 7. An incision through the thyro-hyoid membrane permits by blunt dissection the exposure of the new growth, laryngocele
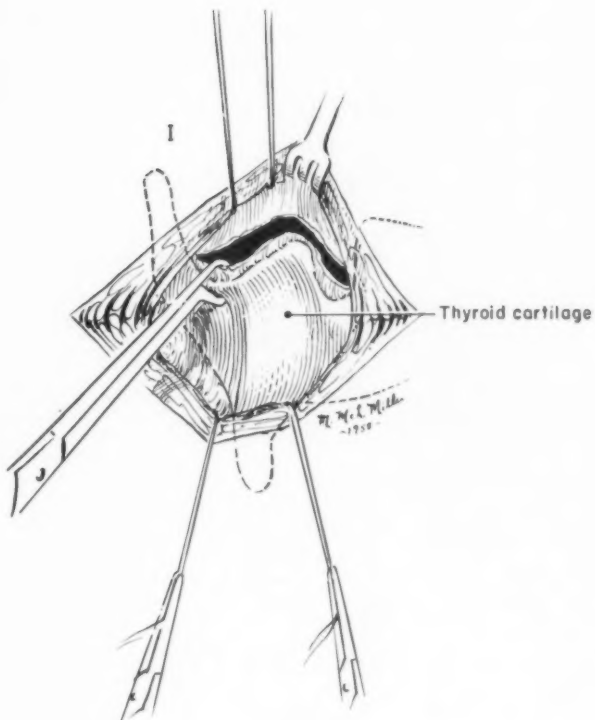
Figure 7

or cyst. If it is a new growth, it is usually encapsulated and shells out very easily.

If it is a laryngocele, after exposure of the fundus, it may be opened, a finger may be inserted into its lumen and the removal accomplished both by sight and by feel. If the laryngocele ends by a stalk it is ligated and inverted.

If the growth is a cyst, after exposure it may be aspirated, first by syringe, then by opening the cyst at its fundus, emptied by suction
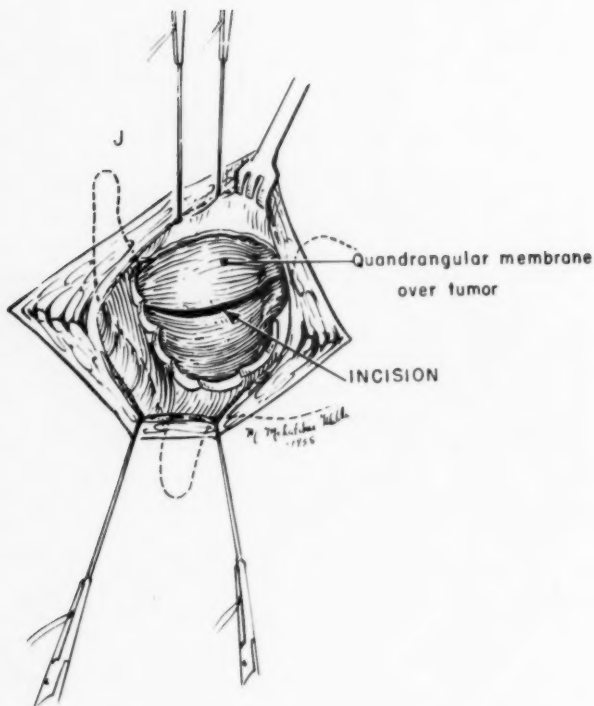
Figure 8

tube. When the contents of the cyst are evacuated, it is treated as a laryngocele.

One advantage of the palpating finger, besides facilitating the dissection of the laryngocele or of the cyst, is that you can feel not only the arytenoid cartilage, but the true vocal cord, so that orientation is perfect at all times.

Step 8. The cut omohyoid and sternohyoid are approximated and the long sutures which were used as retractors are tied. A soft

Figure 9
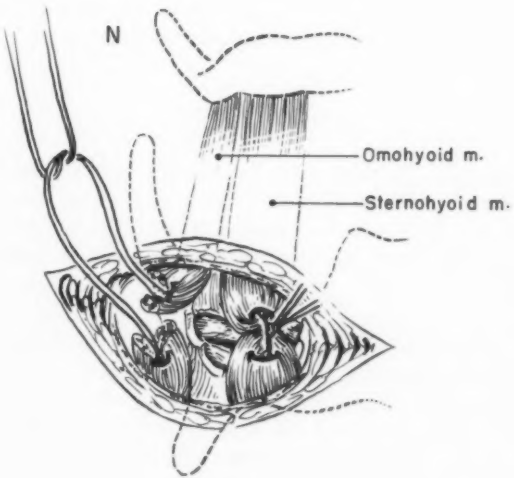
Figure 10

Figure 11

rubber drain is inserted and the incision is closed by your favorite method. The tracheotomy tube is usually removed in 24 to 48 hours.
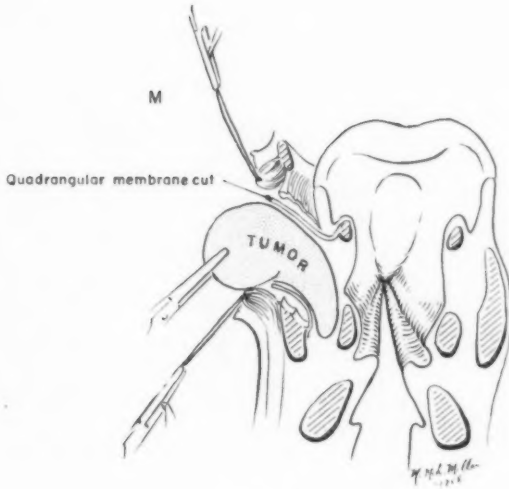
REPORT OF CASES

Since October of 1957 I have used this approach in four cases, the first in a 30-year-old housewife who knew that something was wrong with her larynx for ten years. The biopsy, under suspension laryngoscopy, was unsatisfactory, but the specimen on removal was a neurofibroma.

Case 2 was a 49-year-old woman who had been in and out of the Massachusetts Eye and Ear Infirmary for the past 20 years without a satisfactory biopsy of the large, smooth mass involving the left aryepiglottic fold. Some years ago when she was on my service and I attempted a biopsy under Lynch suspension, I almost lost her because of hemorrhage. At operation on February 18, 1958, by this approach, the growth proved to be a chemodectoma.

Case 3 was an internal laryngocele in a 61-year-old male and Case 4 was a cyst in a 71-year-old woman with laryngeal symptoms for two years and in respiratory distress upon admission.

Case 5 was that of Dr. George F. Reed, that of an external laryngocele in a 62-year-old male.

The advantages of this operation are:

1. It gives adequate exposure.

2. It is direct.

3. There is no intralaryngeal trauma.

4. There are no intralaryngeal complications.

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CARCINOMA OF THE NASOPHARYNX

AN ANALYSIS OF THIRTY-FOUR CASES AND A PRELIMINARY REPORT ON PALATAL FENESTRATION IN ITS MANAGEMENT

L. Q. PANG, M.D.

(by invitation)

HONOLULU, HAWAII

Carcinoma of the nasopharynx is the most malignant of all tumors of the upper respiratory and alimentary tracts. Yet, it is one that is most frequently missed in its early stages. It has been variously estimated that in the average case the patient will have symptoms for three months before consulting the physician. After this, it takes another four months before the proper diagnosis is made. During this time, many unnecessary surgical procedures and often, more than one in a case will have been made. By the time the correct diagnosis has been made, symptoms of metastases may be the predominant clinical feature.

This appears to be a serious indictment against the physician. However, the early diagnosis is indeed a difficult problem. Unless one is constantly alert to its early symptoms and manifestations, and keeps this condition constantly in mind and makes an all-out attempt to prove his suspicions, it can very easily be missed.

This is illustrated by my very first case of carcinoma of the nasopharynx which stands out very vividly in my mind. During the first year of my practice, a middle aged Chinese woman consulted me for a feeling of fullness in her right ear. The only positive finding was a moderately dull and retracted right ear drum. I catheterized her right eustachian tube several times and felt rather proud that I was able to give her symptomatic relief. Imagine my chagrin when I

was informed by her husband, nine months later, that she had a cancer of the throat and was not expected to live very long.

This paper presents my experiences and reviews those of other authors. An analysis of my series of thirty-four cases and a preliminary report on my experiences with palatal fenestration in the management of these cases will be presented. Statistically, this small series may be insignificant. However, it is interesting how my limited experience corresponded in many respects with those of other authors with much larger series.

INCIDENCE

The reported incidence of carcinoma of the nasopharynx varies with different authors. Various authors[1-3] estimate that it makes up from 1 to 3% of all malignant growths. Omerod[4] found that it comprises 8% of all the malignancies seen in the otolaryngological clinics in Great Britain. Shu Yih and Cowdry[5] state that it is the most frequent malignancy seen in the Chinese male and the next most frequent in the female in Formosa. At the Queen's Hospital in Honolulu, it made up 5.8% of all head and neck malignancies admitted for a period of the last four years. At the St. Francis Hospital, for the same period, it was 3.5%. In my own personal experiences, it is by far the most frequent malignancy of the head and neck.

RACE

It has always been a well known fact that the Chinese are the most susceptible to this disease. Shu Yih and Cowdry[5] state that in Formosa, it ranks second in frequency to cancer of the genital organs. However, in males, it ranks first. Martinez,[6] in a report of sixty-four cancer cases among the Chinese observed in Cuba, found that 20 (31%) had carcinoma of the nasopharynx. Miller,[7] in a review of 102 cases, found four Chinese (3.9%). Lenz[8] reported an incidence of 6% in his series of 63 cases. Probably, the lowest incidence reported was in that of Simmons and Ariel.[9] They found only one case in Chinese out of a total of 150 cases. Martin and Quan[10] found that in a total of 52 cases of cancer involving the upper respiratory and alimentary tracts in Orientals seen at the Memorial Hospital in New York, 37 cases (71%) were primary in the nasopharynx, and all of these were in Chinese. These 37 cases made up 82% of all the head

and neck cancers seen in the Chinese as in contrast with the 5.5% seen in the over-all Caucasian population. Incidentally, in this series, there were three females (8%) as compared to the 20% incidence in the Caucasian females. However, their most striking statement was that they had never seen a case of carcinoma of the nasopharynx in an American-born Chinese. All their cases were in Chinese who had migrated to America and had lived many years under American standards of diet, hygiene and sanitation. This statement was made to refute the environmental factors as a causative factor and to hold that the tendency is racial and inherited. This amazing statement is certainly contradictory to my experience.

In my series of thirty-four cases, there were twenty-seven Chinese (80%), four Filipinos (11.7%), two Japanese (6%), one Korean and one Caucasian. Of the twenty-seven Chinese, nineteen (70%) were in males and eight (30%) were in females. Sixteen (60%) of the Chinese were born in America as contrasted with the series of Martin and Quan.

All these Chinese were originally from South China or were offsprings from those who had migrated to Hawaii from South China. This fact is mentioned because in my conversations with many of the otolaryngologists from China, the fact was brought out that carcinoma of the nasopharynx does not occur as frequently in the Northern Chinese. To date, I have not been able to get any definite statistics to prove this statement.

AGE

The average age in this series was forty-four years. The youngest was twenty-five years, and the oldest, sixty-seven years of age. Seven (21%) were below the age of thirty. This corresponds with the experiences of Martin[2] who states that carcinoma of the nasopharynx occurs more often at an earlier age below thirty years and is found more often in children than any other malignant growth of the upper respiratory and alimentary tracts. In his series, 20% of the patients were below the age of thirty.

FAMILIAL TENDENCIES

Nothing has been written regarding familial tendency. There were two instances in my series where more than one member devel-

TABLE I

LIST OF SYMPTOMS IN ORDER OF FREQUENCY
IN THIRTY-FOUR CASES

1.	Enlarged cervical nodes—unilateral	22	(65%)
2.	Unilateral nasal obstruction	15	(45%)
3.	Bloody nasal discharge	14	(41%)
4.	Head and neck pains	12	(35%)
5.	Tinnitus	11	(33%)
6.	Secretory otitis media Primary 3 cases Subsequent 6 cases	9	(26%)
7.	Blockage of ears	7	(21%)
8.	Diplopia—Lateral rectus paralysis NVI	7	(21%)
9.	Involvement of NV	5	(15%)
10.	Trismus	5	(15%)
11.	Bilateral neck nodes	2	(6%)
12.	Ptosis	2	(6%)
13.	Ophthalmoplegia	2	(6%)
14.	Asymmetry of palate	2	(6%)
15.	Epistaxis (primary)	1	(3%)

oped the disease. One instance involved a mother and her son. The other instance involved a sister and a brother. This is an incidence of slightly over 10%. However, this may be purely coincidental.

SYMPTOMS

The predominating symptoms in the order of frequency were 1) enlarged cervical glands; 2) unilateral nasal obstruction; 3) bloody nasal discharge; 4) hissing tinnitus; 5) feeling of blockage in the ear; 6) impaired hearing; and 7) head and neck pains.

Metastatic cervical nodes were present in twenty-two (65%) of the cases (Table I). The glands most frequently involved were

those below the angle of the jaw (the so-called tonsillar glands) and those beneath the upper attachment of the sternomastoid muscle. It has become my dictum that any case with an enlargement of these nodes will be considered as a case of carcinoma of the nasopharynx until proven otherwise. Occasionally, the spinal accessory nodes may be the first to be involved. While it has been said that the submaxillary nodes are rarely involved, they were involved in two of my cases. Two cases had bilateral neck nodes when first seen. Contralateral neck nodes developed in six cases (18%).

A unilateral nasal obstruction was the primary symptom in fifteen cases and a bloody nasal discharge was noted in fourteen cases. A primary nasal hemorrhage was present in only one case.

Ear symptoms are a prominent features in this disease. In my mind, a hissing type of tinnitus is probably the earliest symptom. It preceded the enlargement of the cervical nodes in 50% of the cases. It is an early symptom in 30% of my cases, but I feel that a careful history may reveal a higher incidence. A feeling of fullness or blockage of the ear was present in seven cases (21%). Impaired hearing was a predominant symptom in two cases. A secretory otitis media was present or subsequently developed in 27%. The ear symptoms are such a predominant part of the clinical picture that a careful nasopharyngeal examination is imperative in all these cases. In these cases, the lesions are more likely to be found in the lateral wall in or near the fossa of Rosenmüller.

Intracranial metastases occurred in sixteen cases (47%). Of these cases, less than 50% showed radiologic evidence of destruction of the base of the skull. Cranial nerve involvement was not uncommon. A lateral rectus paralysis (N VI) occurred in seven cases (21%). The V nerve was involved in five cases (15%). Third nerve involvement was seen in two cases (6%). A jugular bulb syndrome was seen in one case. In this case, the involvement of the IX, X, XI, and XII cranial nerves caused a hoarseness due to the vocal cord paresis, a paresis of the palate, nasal regurgitation of food and a unilateral deviation and paresis of the tongue. A drooping of the ipsilateral shoulder did not occur.

Intraorbital extensions occurred in two cases causing an exophthalmos and ophthalmoplegia. In one case, the vision in the eye was completely destroyed.

In five cases (15%), there was an extension of the lesion along the pterygoid process to involve the internal pterygoid muscle and cause a trismus. In two of these cases, there was further extension into the palate to involve the levator palatini muscle and cause a bulging and asymmetry of the soft palate with a subsequent nasal voice.

While the sinuses may become infected because of the obstruction to drainage, actual extension of the lesion to the ethmoids is rather uncommon. This occurred in only one case. The lesion in this case was situated high in the nasopharyngeal vault and extended into the ethmoid cells and into the retrobulbar area causing a lateral rectus paralysis, severe headache and retrobulbar optic neuritis which produced a scotoma in the visual field. There was a question here whethed there was an intracranial metastasis. However, a fenestration of the palate, electrocoagulation of the lesion, and an exenteration of the ethmoid cells followed by deep x-ray therapy completely cleared up the symptoms. While the local lesion was controlled, the patient died of distant metastases in seven months.

Distant metastases occur more frequently than any other malignant lesion of the upper respiratory and alimentary tracts.[2,9] The metastases occur below the clavicle in one-third of the cases. In this series, distant metastases occurred in seven cases (26%). In one of these cases, an autopsy revealed an interesting complication of therapy. In addition to the metastases to the cervical nodes, the lungs, the liver, and the skeletal structures, a softening of the left frontal lobe of the brain was found. This softening was due to an irradiogenic necrosis.

DIAGNOSIS

Most authors[3,9,11-13] have decried the fact that the diagnosis is made late when metastatic symptoms predominated the clinical picture.

In this series, the average length of time from the onset of symptoms to the actual diagnosis averaged 6.1 months. Several reasons are responsible for this delay. The first is the relative lack of early symptoms related to the primary lesion. The second lies in the inability of the physician to make an early diagnosis. This is illustrated by the following cases.

In two instances, a septal resection had been done for relief of nasal obstruction. In one case, the patient had been under observa-

tion for an occipital headache for one year. He was seen by an
internist, an ophthalmologist, a neurosurgeon, and two otolaryngolo-
gists. He was diagnosed as a psychoneurotic.

In three cases, the patients had been treated by otolaryngologists
for several months for a sinusitis before consulting me. In two in-
stances, the patients refused a biopsy and consulted other otolaryngol-
ogists. One was treated for eight months and the other, for eighteen
months for a sinusitis before returning for the biopsy. In another
case, my first biopsy was negative. The patient refused to have
another biopsy and she was treated by another otolaryngologist for
a gumma of the nasopharynx because she had a previous history of
lues and a positive Wasserman. She returned six months later. Two
more biopsies were necessary before a positive diagnosis was made.
In another case, a carcinoma of the nasopharynx was suspected. Two
biopsies were negative. The patient returned twenty months later
with an enlarged node in the neck which proved to be a metastasis
to a lymph node. Two more biopsies were necessary to prove the
diagnosis. These last two cases are cited to illustrate the occasional
difficulty in making the diagnosis and the necessity of repeated
biopsies if there is any suspicion.

Probably the most common error is in the cases where tinnitus
or a feeling of a blocked ear is the early symptom. In six cases,
catheterization of the eustachian tubes had been carried out for relief
of the symptoms. In one case, a hearing aid had been prescribed
because of a conductive deafness involving both ears. This deafness
was caused by a secretory otitis media.

The early diagnosis will depend upon 1) a high degree of sus-
picion; 2) a careful examination and a visualization of the entire
nasopharynx of any patient presenting the symptoms enumerated
above; and 3) a biopsy of any suspected lesion.

Of course, the most ideal practice is to examine the nasopharynx
of every patient regardless of the otolaryngolic complaint. The
most efficient method of examining the nasopharynx is by use of the
nasopharyngeal mirror. In 10% of the patients, a spray of 2% pon-
tocaine is necessary to eliminate the gag reflex. In a small percentage
of cases, this examination cannot be done and the use of a naso-
pharyngoscope is necessary. The examination with the nasopharyngo-
scope is not as satisfactory as that with the mirror in that it gives

only a limited view of the nasopharynx. However, it is a great help in visualizing the lesion once it has been spotted by the mirror. Probably its greatest use is its aid in doing a biopsy.

Palpation of the nasopharynx is unsatisfactory because it is uncomfortable to the patient. Furthermore, most of the lesions are so small that they are not easily felt. If palpation is to be done, it should be done under general anesthesia.

X-ray visualizatoin of the nasopharynx has not been used in this series. Most of the lesions can be visualized with the mirror or nasopharyngoscope. An x-ray of the base of the skull is recommended in cases where intracranial extension is suspected.

In early cases, ulceration may not be present. The only noticeable lesion may be a slight nodular irregularity in the wall. In some cases, the fossa of Rosenmüller may be partially obliterated by irregular tissue simulating lymphoid tissue.

Every suspicious lesion in the nasopharynx should have a biopsy. In our series, it was done under local anesthesia. The use of general anesthesia is not only unnecessary but makes the procedure more difficult and complicated. It is extremely difficult to visualize a lesion in this area through the mouth even if a palate retractor is used. I mention this because I have seen several cases done under general anesthesia. An unsatisfactory biopsy was the result in most of these cases and the procedure had to be repeated under local anesthesia.

It is needless to say that biopsy should be repeated as long as there is any suspicion of a malignancy. Several of my cases required repeated biopsies and, in one case, four biopsies were necessary to prove the diagnosis. This is not surprising as the nasopharynx is so often overgrown with hypertrophied lymphoid tissue or granulation tissue that it is very easy to remove these tissues instead of the lesion. Whenever a pathologist fails to find neoplastic changes in the biopsy material but finds ulceration, necrosis or significant adenoiditis, repeated biopsies and additional sections are especially indicated.

PATHOLOGY

As far as I am concerned, carcinoma of the nasopharynx is synonymous with cancer of the nasopharynx. In my series of thirty-

six cases of cancer of the nasopharynx, thirty-four (94%) were carcinoma. The other two were a case of lymphosarcoma in a four year old Caucasion-Hawaiian boy and a chordoma in a 40 year old Filipino female.

Histopathologically, the transitional cell carcinoma made up more than 50% of the cases. The next in frequency was the lympho-epithelioma or so-called Schmincke tumor. While some authors tend to give some prognostic significance to the different histopathological picture, I have not been able to confirm this in my series.

TREATMENT

The universal treatment is irradiation.[17] In all my cases, deep x-ray therapy was used by the radiotherapist. Under this therapy, the lesions in the nasopharynx and the cervical glands virtually melt away. There is improvement in the symptoms and the general health of the patients. Unfortunately, while the lesions are radio-sensitive, they are not radiocurable. A few patients developed metas-tases to contralateral neck glands even under treatment. A recur-rence of the local lesion developed in over 50% of the cases. Unfortu-nately, the recurrent lesion became progressively more radioresistant with each recurrence. The recurrences were treated by the use of intracavitory radium with or without deep x-ray therapy.

NECK DISSECTION

While all agree that the treatments of carcinoma of the naso-pharynx is irradiation, no such unanimity of opinion exists regarding the management of the cervical metastases. Martin[2] feels that neck dissection is of no value because the primary lesion is usually a highly malignant anaplastic growth which tends to metastasize early and widely and may metastasize to both sides of the neck. He feels that irradiation is capable of permanently controlling a fair percentage of the cervical metastases. This probably represents the majority opinion.

Henry Woo[14] of San Francisco feels that a neck dissection in selected cases is of benefit. Although his series is small (20 cases), he feels that almost all the patients with cervical metastases succumbed in two years following the conventional deep x-ray therapy. He

cites a case in which there had been irradiation at the University of California, but the glands increased in size and number. Because no other therapy was available, a neck dissection was performed. The patient survived eight years and has no recurrence to date. He feels that while the neck dissection is not an en bloc dissection of the lesion, all modes of treatment should be considered in any one patient. The x-rays must be relied upon to control the primary site and intervening pathways. He also cites several cases in which no clinically palpable nodes were present. Yet, the nodes in the resected specimen were heavily involved by tumor cells. This, to him, suggests that performing a neck dissection in these early cases may help in preventing cervical metastases.

In my series, there were five cases in which a radical neck dissection was performed. Three of these cases were done elsewhere. Two of these cases were done for a contralateral cervical metastases. The patients died within eighteen months from intracranial and generalized metastases. The third patient had an ipsilateral neck dissection but died in one year from generalized metastases and a rupture of a large vessel in the neck.

The two cases performed by me were interesting. Both had deep x-ray therapy for the primary lesion and cervical metastases. However, it was felt that there was an involvement of the glands because of a residual swelling of the "tonsillar gland" at the angle of the jaw. A neck dissection was decided upon after consultation with the radiotherapist. A careful microscopic examination failed to reveal any residual carcinoma in the neck contents. The deep x-ray therapy had evidently destroyed all the tumor cells. Both are alive after two and a half years, although one patient had a local recurrence which was controlled by intracavitory irradiation.

From my limited experience, I feel that a neck dissection may be of benefit only in those cases where the primary lesion is definitely controlled by the irradiation. These cases, I am convinced, will be few in number since the rate of local recurrence in my series is over 50%.

PROGNOSIS

Carcinoma of the nasopharynx carries a high mortality. In a review of the literature, the prognoses ventured by the various authors

range from sheer desperation to optimism. Martin[2] reported a net five-year cure rate for all patients of 25% in a series of eighty-seven cases. He states that in patients without cervical metastases at the time of admission, a cure rate of 50% is possible. He also states that the prognosis is worse in the young and in the aged. In the young, distant metastases often occurred even with treatment. Lenz,[8] in 1942, reported a 27.6% five year cure in a series of forty-four cases regardless of the stage of the disease. New and Stephenson[11] reported that of 234 patients, only 13% were living after five years. Furstenburg[15] reported in 1938, that only one of his forty-two patients was alive after two years. Schall[17] reported a 28% five year cure in 102 cases.

In my series of thirty-four cases, twenty-two patients have died of the disease. The average length of life in these cases was twenty-nine months. Of these twenty-two patients, one died six years, one died five years, three four years, seven within two and one-half years, seven within one and one-half years and three in less than one year after the discovery of the lesion. In the three who died in less than one year, the average age was thirty-two years.

It is interesting to note that two patients died of the disease after living over five years. One died after six years, and the other after five years, of intracranial extension. Godtfredsen[16] has contended that in carcinoma of the nasopharynx, a cure cannot be definitely declared complete until the patient has been free of symptoms for at least nine years.

Of the remaining twelve cases, one has gone over fourteen years without any signs of recurrence. One has gone over seven years. This case is interesting because the only treatment the patient had was two x-ray treatments. He refused further treatments and used only Chinese herbs. He now has involvement of the base of the skull but appears to be free of symptoms after a course of deep x-ray treatments. Two cases have gone over six years. Of these, one developed a recurrence after the fourth year. This appears to be controlled by further deep x-ray therapy. Two cases have gone over two and a half years. These are the cases in which a radical neck dissection was done. One had a recurrence which is apparently controlled by intracavitory irradiation. All the other cases are less than one year in duration.

In summarizing my results, there were six cases (17.5%) of five year survivals. However, two of these patients developed recurrences and intracranial metastases and died. This leaves only four cases or a six year survival rate of 12%.

PALATAL FENESTRATION

In the irradiation of the nasopharynx, the chief difficulty is the inability of the radiotherapist to clearly visualize the lesion and thus accurately determine the size and extent of the lesion. He is unable to check the accuracy of the beam and the measurement of the dosage and to observe the effect of the irradiation upon the tumor during the treatment. Furthermore, he is unable to satisfactorily carry out the routine follow-up examination of the irradiated area. He must depend upon the otolaryngologist. Even the latter may have difficulty in examining the irradiated nasopharynx because of the intense reaction of the irradiated area and the pain and discomfort accompanying it. Then there are cases in which a repeat biopsy is necessary after the conclusion of the deep x-ray therapy. The same difficulty applies in cases in which supplementary intracavitory irradiation may be necessary.

Several operative procedures have been devised to overcome these difficulties. Hara,[3] in 1954, described a transpalatal approach for the surgical extirpation of certain types of nasopharyngeal tumors and malignancies and to facilitate its follow-up examination. The primary principle of his operation was to remove enough of the posterior portion of the hard palate and the vomer so that the soft palate could be retracted forward with a catheter inserted through the nose and delivered through the mouth. With gentle traction on the catheter, the soft palate can be retracted forward to expose the nasopharynx and give an adequate view of the operative field.

Sooy[18] treats his cases of recurrent carcinoma of the nasopharynx by electrodesiccation and local intranasal application of radioactive cobalt. In order to get a better view of the nasopharynx, and more space for transnasal manipulation, a greater portion of the septum is removed. The electrodesiccation is carefully done to produce a slough of only 1.0 centimeter of bone and muscle. The radioactive cobalt is applied at 1.0 centimeter distance from the area via a Foley catheter. The bag is distanded with radio-opaque solution to permit

TABLE II

RESULTS IN THIRTY-FOUR CASES

I.   DEAD—22 CASES

A.   Average length of life—29 months

B.   Individual considerations

1.	After 6 years	1 case
2.	After 5 years	1 case
3.	After 4 years	3 cases
4.	Within 2 to 2½ years	7 cases
5.	Within 1 to 1½ years	7 cases
6.	Less than 1 year	3 cases
	a. (Average age of this group—32 years)	

II.   ALIVE—12 CASES

A.   Individual considerations

1.   After 14 years—1 case

2.   After 7 years—1 case - now being treated for disease;
     no treatment until after 5 years

3.   After 6 years—2 cases
     a. 1 case—well with no recurrence
     b. 1 case—had recurrence after 4th year; now apparently
         well

4.   After 2½ years—3 cases - two cases with neck dissection
     a. 1 case—neck dissection - well
     b. 1 case—neck dissection - recurrence treated by
         intracavitory radium—apparently well
     c. 1 case—has recurrence - dying of disease

5.   Rest of cases—5 cases - less than one year in duration

accurate placement of the cobalt.   The dosage administered was 4000 to 6000 R.   Sooy states that the septectomy affords an excellent view of the nasopharynx.   Although considerable dryness is observed, there is very little crusting after the initial slough and sequestration have been removed.   His report dealt with six cases of which three patients (50%) were alive and free of recurrences more than six years following the procedure.   He has subsequently treated ten more patients with five of them surviving for periods of six months to four years.

Galloway,[19] in a discussion of Sooy's paper, states that he has had the good fortune of seeing some of the cases cured and felt that the combined use of electrosurgery and radium was responsible.

In my series, a local recurrence occurred in over 50% of the cases. This necessitated repeated biopsies and the use of intracavitory irradiation in the treatment of the recurrence. This convinced me that a procedure was necessary so that the nasophahynx could be easily visualized and be approached directly. The best procedure to my mind is a palatal fenestration.

The technique of palatal fenestration used is essentially the one which has been so excellently described by Wilson.[20] The basic principle consists of splitting away the soft palate from the hard palate and removing a sufficient portion of the hard palate and the vomer to create a fenestra that enables one to look directly into the nasopharynx. This fenestra is permanent and is easily covered with a dental prosthesis. This plastic prosthesis is made pre-operatively and is inserted as soon as the patient reacts from the anesthesia. The discomfort is no greater than that involved in the wearing of an upper denture. The prosthesis can be removed and the nose and postnasal cavity can be irrigated periodically with a salt and bicarbonate solution.

To date, four cases have been treated by this method. At the time of surgery, the lesion is electrodesiccated and a 25 mg radium capsule is inserted and held in place by a Foley catheter. A total dosage of 500 mg hours is given. Subsequently, deep x-ray therapy is carried out. While this series is small, the advantages of this treatment are already obvious and both the radio-therapist and I are enthusiastic.

SUMMARY

1. The incidence of carcinoma of the nasopharynx varies from 1 to 3% of all malignancies of the body.

2. The racial incidence is noted. The Chinese appear to be most susceptible.

3. The early diagnosis is difficult and is often missed. In my series of thirty-four cases, the average length of time from the onset

of symptoms to the time the diagnosis is made is six and one-half
months.

4. The most common symptoms in their order of frequency are
1) enlarged cervical nodes; 2) unilateral nasal obstruction; 3) bloody
nasal discharge; 4) tinnitus; 5) feeling of fullness or blockage in the
ear; and 6) headaches. In my mind, the ear symptoms are usually
the earliest.

5. The lesions are usually very radiosensitive, but they are not
necessarily radiocurable. Local recurrences occurred in over 50%
of the cases. Intracranial metastases and generalized metastases are
rather frequent.

6. The treatment is irradiation. The question of neck dissection
is debatable.

7. The transpalatal approach to the nasopharynx in the form
of a palatal fenestration as an aid in the irradiation and in the follow-
up observation and treatment is presented.

8. An over-all five-year remission of 17.5% is reported. This
survival rate drops to 12% at the end of the sixth year.

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THE SIMULATED LARYNX

C. J. Campbell, M.D.
(by invitation)

AND

John A. Murtagh, M.D.

Hanover, N. H.

For centuries man has been interested in making speaking machines. Reviews and bibliographies of this interesting pastime are given by Paget[14] and Dudley and Tarnoczy.[3] Modern instruments are exemplified by the Bell Telephone Laboratories "Voder"[2] and "Vocoder."[1]

What more nearly concerns us is the comparison which has been made of various musical instruments and the larynx by various authors. Pressman,[15] Pressman and Kelemen[16] and Chevalier Jackson[8] comment on past work and present their own theories of vocal cord vibration based on experimental work and clinical observation. Helmholtz[7] in his discussion of reeds and reed instruments considers that the only valid comparison is that between the vocal apparatus and the lips of a horn player. Jackson[8] agrees wholeheartedly with this. Anyone who has listened to the late Dennis Brain, using a horn mouthpiece and a length of garden hose, play a concerto for hosepipe and strings (Angel Recording 35500, The Hoffnung Music Festival Concert) will admit that human lips may perform ably as reeds.

Various people have used the fresh and the preserved larynx removed from the cadavers of human and experimental animals[6,11,13,21] to produce sound by passing air at various flows and at various pres-

sures through the trachea and glottis. Johannes Mueller[6,11] altered the position and the tension of the vocal lips by various maneuvers and noted the changes in the sound produced.

Experiments using a simulated larynx with the "vocal cords" of a frog muscle preparation have been described by Negus.[13] He varied the width of the slit and the stiffness of the muscle by graded electrical stimulation. Jackson[8] describes his observation of his own lips when playing the cornet.

There has been an enormous amount of work done on the production of vowel sounds using mechanical devices. The emphasis has, however, usually been on the resonating cavities beyond the sound emitter. A reed, usually single,[11] a whistle,[10] or a battery of tuning forks[7] has been used to produce the sound. Harmonic analysis of the resulting combination and a comparison with a similar analysis of spoken sounds has been the usual experimental procedure.

An early attempt to produce an apparatus to mimic the motion of the larynx was that of Johannes Muller when, according to Tyndall,[22] he closed the end of a glass tube with two rubber strips leaving a slit between (Fig. 1A). Helmholtz[7] and Muller[11,12] advocated the shape shown in Figure 1B which as Helmholtz states may be blown in either direction. Tyndall[22] states that the simplest reed of this character is made by rolling a rubber membrane around the end of a glass tube leaving about an inch of rubber projecting. By grasping opposite sides of the projecting rubber, stretching it to produce a slit and blowing through the tube, the reed will speak at a pitch which varies with the tension on the edges of the slit. Recent experiments with similar arrangements are those of Svend Smith.[20]

Many workers are very skeptical about the use of models, analogues and similar gimmicks.[12,18] Russell[18] deprecates without reservation such behavior and cites the Rev. Robert Willis[24] who some 125 years ago said (and we quote more fully than did Russell), "just so, musical notes are formed in the larynx in the highest possible purity and perfection, and our best musical instruments offer mere humble imitations of them; but whoever dreamed of seeking from the larynx, an explanation of the laws by which musical notes are governed. These considerations soon induced me, upon entering on this investigation, to lay down a different plan of operation; *namely, neglecting*
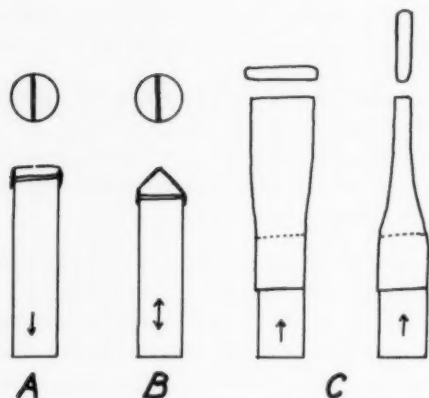
Fig. 1.—Various rubber reeds. A. Attributed to Johannes Muller; B. Described by Muller and Helmholtz; C. Gooch tubing.

entirely the organs of speech, to determine, if possible, by experiments upon the usual acoustic instruments, what forms of cavities or other conditions, are essential to the production of these sounds. . . . " The part in italics only was quoted by Russell.

In order to gain experience with a high speed motion picture camera and also to get a better understanding of the mechanics of vibrating vocal cords, we decided to experiment with simple, inanimate preparations that might mimic or simulate such activity. Considering as did Helmholtz[7] that the vocal apparatus is a double reed, the obvious was to investigate readily available double reeds used in musical instruments. Cf. [24]. The oboe and the bassoon reeds are such choices. (One of us had in the past learned to make such reeds.) The maintenance of proper moisture and temperature, added to the difficulty of devising a satisfactory "embouchure," led to the abandonment of both forms.

The reed ordinarily used in a practice chanter (bag-pipe) is made of plastic, is ordinarily located in a box, is insensitive to changes in humidity, and is usually supplied with an "embouchure" of a small rubber band. It will "speak" without the rubber band, though per-

haps not quite so readily. Moreover, von Kempelen is supposed to have used a bag-pipe reed in his first speaking machine. A copy of the J. Muller (Fig. 1A) reed was abandoned (because of the relatively high pitch for any given diameter of tubing) in favor of that described by Helmholtz (Fig. 1B). Finally the simplest of all was a "reed" made of Gooch tubing (Fig. 1C). This latter had the definite advantage of being readily distorted by a device shown in Figure 2.

For the sake of comparison experiments were run on the Bell Telephone Laboratories Artificial Larynx developed by Riesz.[17]
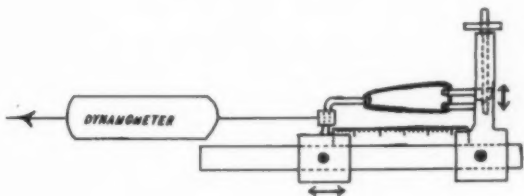

Fig. 2.—Apparatus for imposing tension on Gooch reeds and for making a wedge shaped aperture.

METHODS

The reeds with the exception of those made of Gooch Tubing (Fig. 1C) were usually mounted in a transparent acrylate chamber. Side tubes were arranged for the measurement of input average pressure; rapid changes in input pressure; rapid changes in output pressure; input flow; and sound. If the reed was not mounted in a box, rapid changes in output pressure were measured as sound only (Fig. 3). Resonating chambers attached to the output end of a reed were always simple lengths of thin-walled, rubber tubing of a diameter that would just fit the tube on which the reed was built.

Pictures at ten frames per second were made of the entire set-up. Pictures of the reed, flow meter, and water manometer were made directly through a beam-splitting mirror simultaneously with those of the reflected image of an oscilloscope. The X motion of the oscilloscope spots moved from right to left so that the projected image would apparently move left to right.
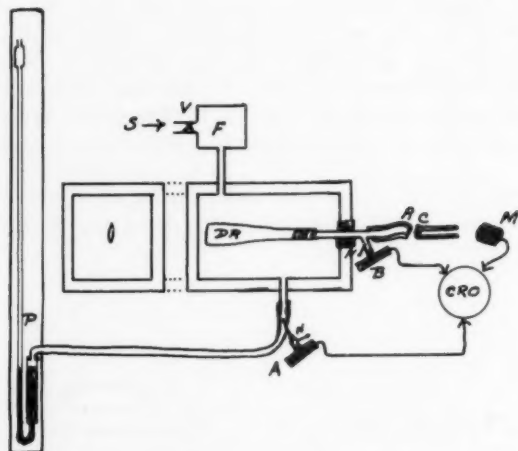
Fig. 3.—A diagram of the usual recording arrangement. A, input, crystal pick up; B, output, crystal pick up; CRO, dual beam cathode ray oscilloscope; DR, double reed; F, flow indicator; M, microphone; N, hypodermic needle leaks; P, water manometer; RC, resonating chamber; S, air supply; V, needle valve.

This procedure merely collected information ten times a second from the various indicators. The image of the reed, if in motion, appears as a blur; but if the movement is at times arrested, or slowed, a denser image is formed.[9] This supplies useful information.

When an attempt to synchronize action and sound was made the framing rate was changed to 16 p.p.s.

For motion analysis the high speed camera (Fairchild HS101) is run at from 500 to 2000 frames per second. Since the reed frequencies have been kept as low as possible these speeds are adequate. When pictures of an actual larynx are made these speeds have been found not adequate and the camera is being rebuilt to run up to 8000 frames per second. Such pictures are usually made with a 6-inch lens and no attempt is made to include the flow meter or manometer in the field. In the interest of keeping illumination and heat as low as possible the beam-splitting mirror is often not used at high speeds. This removes the oscilloscope from the field of view.
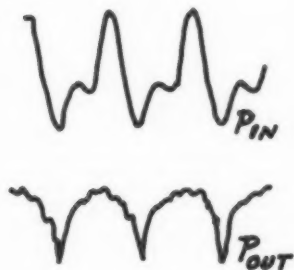
Fig. 4.—CRO tracings from BTL artificial larynx. Pin 2.6 inches of water; frequency 88; length input tube 23 cm; length resonating tube 10.2 cm.
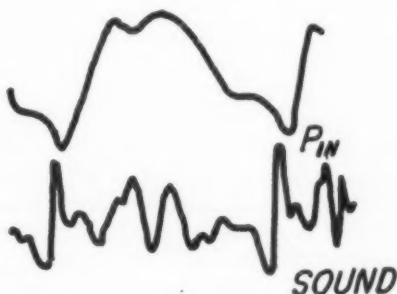
Fig. 5.—CRO tracings from bag-pipe reed. Pin 11.5 inches of water; flow 16.6 cc/sec; length resonator 27.5 cm; frequency 175.

The power requirement of the various reeds was computed by multiplying the input pressure (in dynes per square centimeter) by the input flow in cubic centimeters per second. This product has the dimension of power, a rate of doing work which we have expressed in watts.

Harmonic analysis of the rapidly changing pressures and of sounds is made by putting the output of the transducers (amplified if necessary) through a General Radio 760-B Sound Analyzer.

TABLE I

BTL REED

INPUT LINE		OUTPUT LINE (RESONATOR)	OUTPUT	
MEAN PRESSURE	LENGTH	LENGTH	FREQUENCY	REMARKS
ins. water	cm.	cm.	cycles/sec.	
*4.0	23	5.4	89	*Would not
*4.0	23	0	108	oscillate
3.0	23	7.15	86.5	at 3 inches
3.0	23	10.2	88	of water
3.0	23	34.3	76.5	pressure
4.0	10.2	23	87	
4.0	7.15	23	87	
4.0	23	23	89.5-90	
4.0	34.3	23	92	
4.0	65	23	93	

OBSERVATIONS

The BTL Artificial Larynx. The air supply line and flow meter which worked satisfactorily with other reeds would not actuate the single-reed artificial larynx. However, the reed vibrates readily when, using a short tube one blows one's expired air through it. After a bit of cut and try, we found that the whole input system had to be changed. The flow meter which contained a needle valve had to be removed. An air storage tank was installed in the immediate neighborhood of the reed input and connected to the reed with a relatively short tube. Apparently the input line reactance is important. It was also noted that changes in the input line had as great an effect on frequency (pitch) as changes in the output line (Table I). The effect of changes in input mean pressure is shown in Table II. This undoubtedly also changed the flow. No measurement of flow was made. The rapid pressure changes on the input and output side of the reed at a mean pressure of 2.6 inches of water are shown in Figure 4.

Pictures taken at 1200 frames per second showed that the reed apparently beats against its rubber bed and that its motion probably was not a simple harmonic one. A speed of 2000 frames per second

TABLE II

BTL REED

INPUT PRESSURE	OUTPUT FREQUENCY	REMARKS
2.5	82.	Input line 23 cm long
3.0	84.5	
3.5	86.	Output line 23 cm long
4.0	89.5-90	

showed a definite partial near the outer end of the swing but failed to resolve any other harmonics that might be present.   Harmonic analysis of the rapid input and output pressure changes is shown in Table III for a mean input pressure of 4.4 inches of water.

TABLE III

BTL REED

HARMONIC	RELATIVE AMPLITUDE	FREQUENCY	REMARKS
1	0.575	90	Pin 4.4 inches of water
2	0.94	180	
3	0.375	270	Input line 23 cm
			Output line 6.4 cm
4	1.00	360	
5	0.73	450	
6	0.415	540	
7	0.5	630	
8	0.29	720	
9	0.208	810	
10	0.0083	900	

Riesz[17] gives the power requirements of this device when uttering a sustained vowel sound as approximately 0.06 watts.

The bag-pipe chanter reed was used in the set-up shown in Figure 3.   As mentioned previously it was not at all sensitive to the dimensions of the input line.   As far as we could determine, any length or

TABLE IV

BAG-PIPE REED

HARMONIC	RELATIVE AMPLITUDE			FREQUENCY	REMARKS
	P_{IN}	P_{OUT}	SOUND		
1	1.0	1.0	0.433	56	Average Pin 13.5 inches water
2	0.89	trace	0.075	112	
3	0.666	0.08	1.00	168	Average Flow 33cc/sec
4	0.35	trace	0.865	224	Length of resonator 127 cm
5	0.117		0.43	280	
6	0.073		0.83	336	
7	0.0073		0.06	392	
8	0.073		0.33	448	
9	trace		0.20	504	
10	trace		0.25	560	
11	trace		0.42	616	
12	trace		0.47	682	
13	trace		0.66	738	

diameter of tubing could be used, provided that the necessary pressure and volume could be delivered. The reed speaks only when blown from the front as shown in Figure 3. By attaching to the output end, rubber tubing of various lengths, the reed could be made to sound frequencies of from 54 cycles to 666 cycles. If the resonating tube is made long enough the frequency will again become high and with added length will again run down the scale. Since only random lengths of tubing were used, no serious attempt was made to get the lowest possible frequency from the reed. An example of the wave forms of the rapid pressure changes that were observed are shown in Figure 5. The high harmonic content of the sound is evident. A typical harmonic analysis is given in Table IV. Attention is called to the differences in wave form at various points in the system.

When high speed pictures of the vibrating reed are examined, particularly when the framing rate is high as compared with the frequency of the reed, it is seen that the reed motion is not a simple harmonic one. Successive frames from a single opening and closing of the reed are projected on a drawing board and the outlines of the lips of the reed traced in sequence to give the display of Figure 6. The

TABLE V

BAG-PIPE REED

AVERAGE FLOW	AVERAGE P_{IN}	FREQUENCY	REMARKS
cc/sec	inches water	cycles/sec	
35	10	54	length of
36.6	12	55	resonator 105 cm
37.5	13	56	
	9.5	53	
	11	54.5	
33.3	9.4	52.8-53	

reed in each case seems to follow the fundamental frequency imposed by the resonator. Using a given resonator, changes in flow, which also produce changes in mean pressure, may vary the fundamental frequency over a range of about 5 per cent only (Table V). The number of harmonics present increases with increased flow-pressure.

The power required to actuate the reed has been calculated at various rates of flow, various pressures, for about a dozen frequencies and has been found to range between 0.04 to 0.12 watts.

The Helmholtz type rubber membrane reeds (Fig. 1B) were used in a number of experiments. They were usually blown from behind. Some of the phenomena observed were:

a) the maximum displacement of the reed is often in a direction opposite to the flow of air (the lips actually invert),

b) the output pressure (sound) may change at a rate which is a multiple of the input frequency changes,

c) the movement of the lips is seldom a simple harmonic motion,

d) smoke blown through the reed appears to move in a continuous stream at small amplitudes; in a modulated stream at moderate excursions of the lips; and in discrete puffs at large amplitudes.

The power requirements for these reeds varied directly with the diameter of the tube on which they were formed. Pressures were
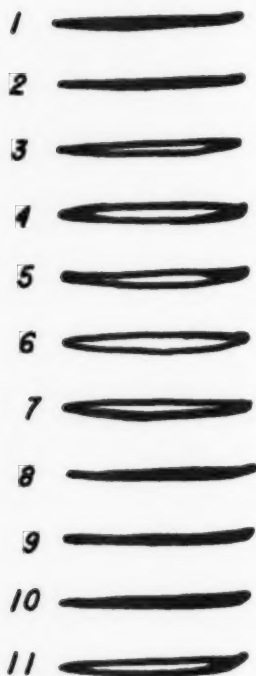
Fig. 6.—The shape of the mouth of the bag-pipe reed in successive frames at 2000 pps.

low and flows relatively high. The calculated power used varied from 0.004 to 0.06 watts.

Gooch Tubing As a Reed. This is perhaps the most interesting of the various things tried. In order to keep frequencies low and to deal with a preparation that could be easily observed, we have used relatively large tubing which has been slightly stretched in placing it over the plastic tubing on which it is mounted. A volume of air greater than could be supplied from the compressed air line is necessary. The "reed" was therefore driven by a small centrifugal blower through a short $1\frac{1}{8}$ inch diameter line. To simplify the
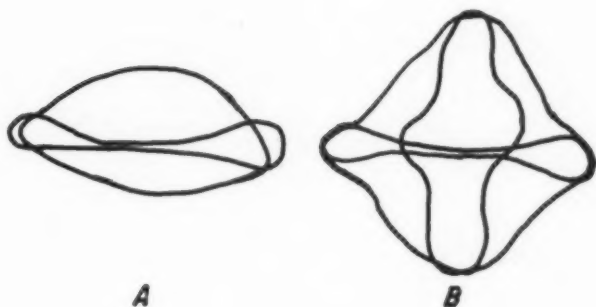
Fig. 7.—Tracings of the dense lines in the blurred (Marey) pictures of the mouth of the Gooch reed.
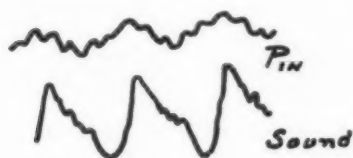

Fig. 8.—CRO tracings from a Gooch reed.

experimental procedure and to avoid resonance effects the reed was operated with the output opening directly into the room. Actually the length of line made no detectable difference in performance unless several feet of tubing were used. The difference then was in the harmonic content only and not in the fundamental. It was more convenient to use a short (5″ rubber tube) line and this was the usual arrangement.

Unless the Gooch tubing was long enough to assume the shape shown in Figure 1C, it would not vibrate. Some forms assumed by the end of the vibrating tubing are shown in the line drawings of Figure 7 made by tracing the projections of selected frames from blurred pictures (Marey) taken at ten per second. In Figure 7A the pressure and flow to the reed are relatively low; in 7B they have
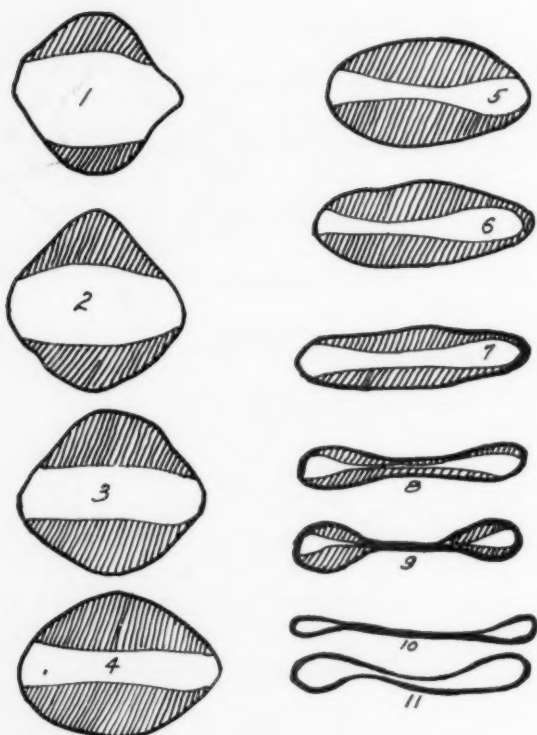
Fig. 9.—Tracings of successive frames of pictures of the end of a Gooch reed taken at 2000 pps. The presenting interior surface of the reed is cross hatched.

been increased and the tube now behaves as a cylinder rather than a reed. If the pressure-flow is increased beyond that in B, the nodes rotate about the ring and moving pictures are required to illustrate the motion.

(When Penrose drain was used instead of Gooch tubing no performance resembling that of a double reed was observed. The rubber vibrated always as a cylinder and it was not necessary to have a length

TABLE VI

GOOCH TUBING
SOUND

HARMONIC	AMPLITUDE		REMARKS
	1	2	
1	.35	.87	Length 2.62 ins. Pressure 1.5 ins.
2	.40	.48	Frequency 75
3	.35	.10	
4	.18	....	
5	.70	.10	1 - Heart Sound Microphone
6	.40	.13	
7	.30	.10	
8	....	....	2 - Fair quality Xtal phone
9	.15	.12	
10	.05	.08	

adequate to give the shape shown in Figure 10. The frequency produced was always low.)

The frequencies generated by the tubing with no modification are always quite low (70-100) with input pressures of from 0.5 to 2.0 inches of water. The wave forms on the input and output (sound) side again differ from one another. The more complicated form (larger number of partials) is on the output side as seen in Figure 8. On the input side the first and fifth harmonics are the only ones apparent on inspection; in the output no analysis is possible on inspection. An analysis, on another occasion, of the first ten partials of the sound is shown in Table VI. Also included is a comparison between a microphone intended for clinical recording of heart sounds and a fair quality crystal microphone. Used in the room the heart sound microphone appeared to be resonant between 200 and 500 cycles and was abandoned for further use.

In examining pictures taken at 2000 frames per second of the open end of the "reed," one's attention is immediately drawn to the appearance of a concavity or bulge inward which forms near the base of the reed and moves toward the open end, nearly filling the lumen as it advances. Outlines of the projected images of successive
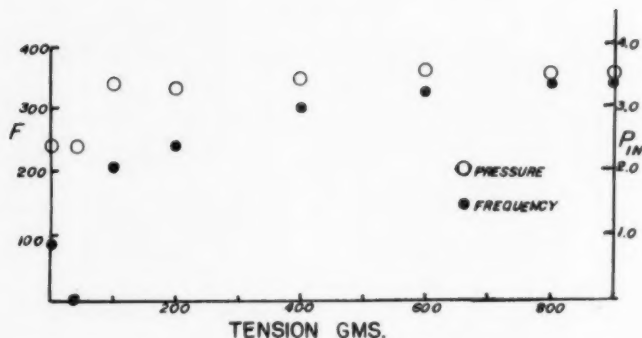
Fig. 10.—Gooch reed. Tension vs. frequency and input pressure.

frames (the bulging interior surface is cross hatched) are shown in Figure 9. These begin with the frame in which the bulge is first obvious and run through the closing and the beginning of the opening of the reed. The sequence lasts some 0.0055 seconds.

When photographs are made from above and from the side, this inward bulge is seen to form in the region where a throat exists in the tube (Fig. 1C) and to run as a wave to the open end. What is even more interesting is that a smaller wave is reflected from the open end and runs toward the base arriving at the throat just in time to aid (or to initiate) the formation of another larger wave which sweeps toward the open end.

This has the appearance of a positive feed back which would establish sustained oscillation. The Bernoulli effect and the feed back were postulated by Wegel in his theory of vibration of the larynx.[23] The increased velocity of the air passing through the throat apparently reduces the pressure within the tube at that point and permits the atmosphere to press the wall inward. This depression moves as a wave whose velocity is probably a function of the relation of the stiffness to the mass of the walls of the tube. Arriving at the open end, the wave first closes and then flips the edges outward and starts the small return wave.
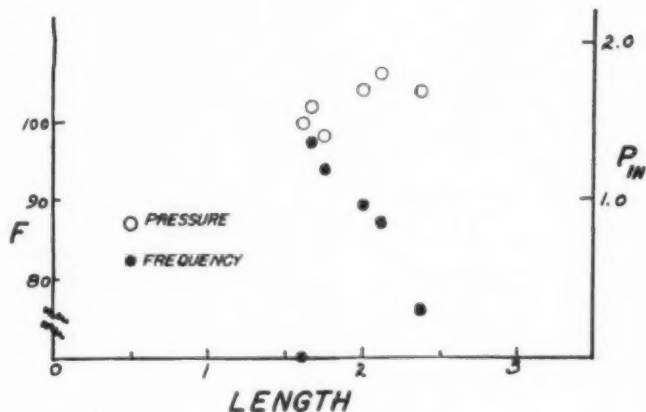
Fig. 11.—Gooch reed. Free length in inches vs. frequency and input pressure.

When the stiffness of the tube walls was increased by elongating and by applying tension (using the apparatus shown in Figure 2) the results shown in Figure 10 were obtained. Contact of the prongs with the tubing apparently stops vibration until the applied tension is of the order of 100 grams. Then the frequency jumps a full octave but the maximum increase obtained with any tension that does not rupture the tube is no more than a twelfth.

When the prongs on the right (Fig. 2) are separated to form a wedge shaped opening, one can, by opening the base of the wedge, prevent the increase in velocity necessary to start oscillation. With the reed vibrating the amplitude of oscillation diminishes to nil as the prongs are separated. The separation required diminishes as the tension on the tube is increased. There is very little frequency change as the wedge is varied.

In an attempt to find the cause of changes in frequency, high speed pictures were made of the Gooch reed with various lengths free beyond the end of the rigid tube. With no tension on the reed it was found that the seven-eighths inch tubing would not oscillate with less than 1.6 inches protruding. As the tube was lengthened the locus
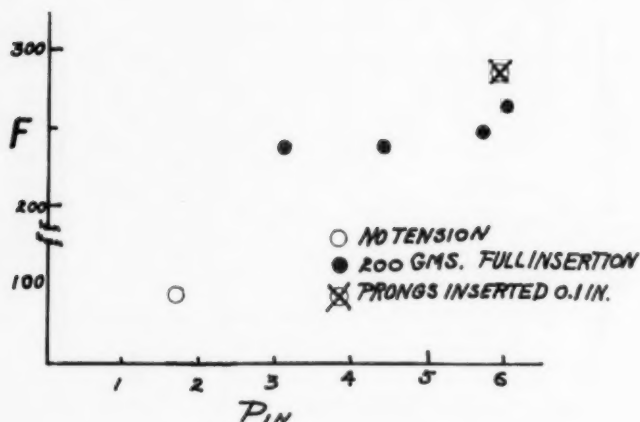
Fig. 12.—Gooch reed.   Free length 2 inches.

of formation of the inward bulge moved away from the free end and the frequency of vibration diminished with very little mean pressure change.   Expressed differently, the time required for the formation of the depression, for the sweep toward the open end, and the return of the smaller depression increased as the free tube length increased over a limited range (Fig. 11).

With the length held constant, and a constant tension applied to the tube, the effect of changing the average input pressure was tried (Fig. 12).   Until the input pressure became excessive there was little change in frequency.   With an input pressure of about 6 inches of water the activity of the reed became very complicated.   When the prongs were inserted a minimal distance (0.1 inch) a pressure of 5.9 inches was required to start oscillation; the Gooch tubing was distended and executed a very complicated pattern of vibration. Apparently the location of the Venturi-like throat and the velocity of propagation of the inward bulge may be considered to determine the period of oscillation.   The pressure of incoming air and the tension on the lips, beyond a minimum to establish adequate stiffness, have only second order effects on the frequency of the sound produced (Fig. 13).

$$\text{PERIOD} = \frac{2L}{\text{VELOCITY}}$$

$$\text{FREQUENCY} = \frac{\text{VELOCITY}}{2L}$$

$$\text{VELOCITY} \propto \sqrt{\frac{\text{STIFFNESS}}{\text{MASS}}}$$
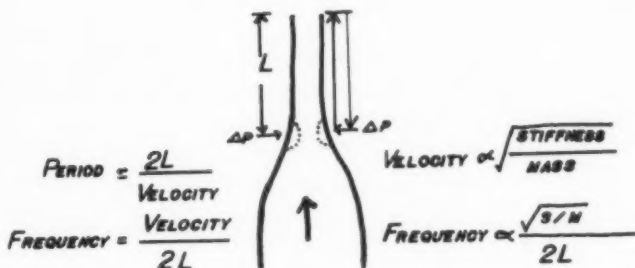
$$\text{FREQUENCY} \propto \frac{\sqrt{S/M}}{2L}$$

Fig. 13.—Diagram of factors operating to determine motion of Gooch reed.

The power required to operate the Gooch tubing as a reed varied between 0.01 and 0.04 watts when the tube was vibrating as a reed.

COMMENT

Since no attempt was made to mimic closely either the form of the larynx or the sound produced by it, the relatively complicated Polsterpfeifen of Ewald[4,4a] were not used. In view of the results obtained with Gooch tubing it might be an interesting thing to do. Some relatively recent experiments with the cushion pipe are reported by Carhart.[5] The infraglottal resonance was the phenomenon investigated rather than the movement of the glottic lips. Holmes[5a] using a different model larynx has reported a similar investigation.

None of the models examined have any but a general resemblance to the glottis (they are all double reeds). The sounds produced by the bag-pipe reed and the Helmholtz type rubber reed resemble voices of a sort. The latter might be a serviceable crow call. The Gooch tubing, however, was selected because of the resemblance of the drape of the rubber on the mounting tube to the shape of the infraglottal regions of the larynx.

We have gained experience with the high speed camera and have obtained objective information on matters which to us had been unclear and in many instances seemed based on speculation. The behavior of the Gooch tubing as seen in the 2000 p.p.s. motion pictures may help explain the astonishing "all aluff" appearance of the

vocal cords in some of the Bell Laboratories motion pictures.[25]   Smith
uses the term "most incredible" in his discussion.[19]

We do not agree with Trendelenburg and Wullstein[21] in that
the cavities beyond the reed (vocal cords of cadaver) have no effect
on the manner of vibration of the reed.

SUMMARY

A difference in wave form has been observed on the input and
output sides of all systems examined.

With a resonator in the output line, the frequency of the output
wave may be a multiple of that of the input.

With double reeds of high compliance (small stiffness) the reso-
nance of the output line determines the fundamental frequency of
vibration.   The motion usually is not a simple harmonic one.

In the double reed systems examined the length and size of the
input line made little difference as long as adequate flow and pressure
were supplied.

The small effects of pressure and flow and the relatively modest
effects (Gooch tubing only) of tension changes on fundamental
frequency have been demonstrated.

The power requirements of the various systems tried correspond
with those generally calculated for the conversational range in
humans.

The existence of a pressure lower than that of the surrounding
atmosphere has been shown in the Helmholtz and the Gooch tube
reeds.

The existence of a feedback to maintain vibration has been
shown in the Gooch tubing.

The importance of size and of internal configuration on the
input side of the vibrating lips has been demonstrated in Gooch
tubing (Fig. 13).

CONCLUSION

The application of the information gained to experimental work on animals will result in our paying increased attention to the subglottic structures. The larynx should be examined (photographed) from the input side (as well as from above) to determine, if possible, the effects (on frequency, wave form) of changes in the dimensions and contours of the inferior surface of the glottis (Fig. 13). These may afford a rational basis for the known complex structure of the thyro-arytenoid muscle. The actual subglottic shape of this muscle may be the primary determinant of frequency of vibration of the vocal cords.

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XXX

SURGERY OF THE NECK
FOLLOWING RADIATION THERAPY
FOR CANCER

WALTER P. WORK, M.D.

SAN FRANCISCO, CALIF.

It is the purpose of this discussion to present our surgical experiences in 22 patients who received x-ray therapy as the initial treatment for primary carcinoma of the larynx or pharynx. In all cases the irradiation was reportedly given in tumor doses considered adequate for arresting the disease. However, surgery was carried out because either the cancer was not arrested or because of adverse tissue reactions from the irradiation.

All the patients were males between the ages of 36 to 72 years. Nineteen of the group had primary disease of the larynx while the remaining three patients had primary disease of the pharynx. Squamous cell carcinoma was present in all patients and diagnoses were made by biopsy and microscopic tissue examination.

In 11 cases the primary lesions were cordal, stage I or early stage II, which means that they were ideal for radiation therapy. In the remaining 11 cases the primary lesions were as follows: five lesions were supraglottic (questionable stage), three were pharyngeal (advanced inoperable), and in the remaining three patients the exact site of the primary laryngeal lesion was unclear from the records that accompanied the patients.

The patients received x-ray therapy in at least nine different clinics or offices which meant that at least nine different radiotherapists treated them, probably using as many different techniques. In only one patient was supplementary radiation therapy used in the

form of a cobalt bomb which was placed in the pharynx while the patient was under anesthesia.

The indications for surgery following the x-ray therapy varied considerably in the whole group of patients. For example, in the patients with irradiated lesions wherein the primary disease was not arrested as proven by biopsy and microscopic tissue examinations, the indications for surgery were clean-cut. On the other hand, in those patients where the local laryngeal or pharyngeal tissues showed edema, redness, ulceration and necrosis, the problem of establishing the diagnosis of unarrested cancer was difficult even with repeated biopsies. When the diagnosis of unarrested cancer was finally established, then the indications for surgery in this group were also clean-cut. In other cases where it could not be proven that there was still cancer remaining in the larynx or pharynx, the general status of the patient was often one of the determining factors in the indications for surgery. Inability to swallow, weight loss, cachexia, secondary anemia, vitamin deficiency, hypoproteinemia, repeated bouts of aspiration pneumonia and sepsis were present in varying degrees in some of the patients who had severe local irradiation reactions. These patients often showed no improvement after thorough medical treatment and could only be restored to health following surgery.

CLASSIFICATIONS OF CASES

In order to relate our surgical experiences in these patients, we have divided them into the following groups:

Laryngeal Cancer

Group I. Cancer not controlled by x-ray therapy.

    1. Early cases, nonarrested or recurrence.

    2. Late cases, nonarrested or recurrence.

Group II. Cancer controlled by x-ray therapy, however, complications developed from irradiation.

    1. Early complications.

    2. Late complications.

Pharyngeal Cancer

Group III. Primary cancer partially or fully arrested by irradiation therapy.

In the above classifications it is noted that in Groups I and II, the subgroups in each have the headings of "Early" and"Late." Any period of time under one year following completion of x-ray therapy denotes an "early" case, while any period over one year denotes a "late" case. These are arbitrary periods of time so the cases may be presented conveniently. As a rule one cannot predict early and late recurrences or tissue reactions following radiation therapy.

Widefield laryngectomy was the definitive operation carried out in patients in Groups I and II. Block dissections of the neck were done when indicated, either combined with laryngectomy or at a later date. Plastic operations were done in some cases in multiple steps after laryngectomy, while full thickness sliding skin grafts were used at the initial operation in others. In Group III, several of the patients presented special surgical problems that will be discussed later.

In Groups I, II and III there are 15 patients living and well from five months to nine years postsurgery. Three patients died of other causes one to three years following surgery, while the remaining four died of cancer.

ANALYSIS OF CASES

Laryngeal Cancer

Group I. Wherein the cancer was not controlled by x-ray therapy.

1. *Early Cases of Nonarrested Cancer*

There were nine patients in this subgroup. In only two patients was the primary lesion supraglottic, while in the other seven patients the lesion was cordal in origin, stage I or early stage II. Upon completion of the x-ray therapy varying degrees of hoarseness and soreness of the throat persisted in these cases. Local signs of redness, ulceration and edema of the larynx were evident. Biopsy and microscopic tissue examinations confirmed the persistence of cancer in each patient. The time interval between completion of irradiation and surgery varied from two months to 12 months. Actually, the time interval for most of the patients was under six months. In each patient widefield laryngectomy was performed. In none were modified surgical techniques deemed satisfactory; such as, laryngofissure, hemilaryngectomy, etc. On one patient, who subsequently died of

cancer, bilateral block dissections of the neck were done in two-stage separate operations following laryngectomy.

The technical difficulties encountered in the performance of the surgery in these cases was no greater than in a comparable group of patients who had not been irradiated. Dissection of the tissues was accomplished readily in well-defined tissue planes and bleeding was not excessive. Excessive edema and atrophy of the adjacent laryngeal tissues were not evident.

The low collar incision was used in five cases while the T incision was used in the four others. In only one patient with a T incision was there a small fistula which healed promptly with pressure dressings and the continued use of the nasal gastric feeding tube. In two patients, upon whom a low collar incision was used, there was an accumulation of serum and pus beneath the upper skin flap which when released did not recur and left only small transient sinuses.

It is interesting to point out that some of these patients have developed rather marked radiation tissue changes of the neck; such as, atrophy, pigmentation and telangiectasia which apparently was not influenced by the laryngeal surgery.

There were no special problems in the rehabilitation of these patients and for the most part they developed esophageal speech without difficulty.

Two patients in this group have died of cancer. The other seven are living and are apparently free from cancer. Four are living and well five years or more postsurgery, two are living and well three years or more and one is living and well six months postsurgery.

2. *Late Cases of Nonarrested Cancer*

There were five cases in this subgroup. As in the above subgroup, these cases all showed persistence of squamous cell carcinoma of the larynx sometime after x-ray therapy was completed. However, in contrast to the above patients, these were relatively well from eighteen months to twelve years following irradiation. In addition to the recurrences of cancer locally, one patient showed palpable lymph nodes deep in the left midcervical region of the neck. Further,

skin changes of the neck from radiation therapy were more evident; such as, atrophy, pigmentation and telangiectasia.

It was difficult to ascertain the exact site of the primary lesion in these cases since all were treated initially with x-ray therapy elsewhere. However, on our first examination, it was evident that three of the patients had supraglottic lesions, while the other two had cordal lesions. In one patient with a supraglottic lesion, the lesion was stage III while in the other four patients the lesions were stage II.

The technical difficulties encountered at surgery in this subgroup were more marked than in the patients of subgroup 1. The tissue planes were less evident and there was more edema and atrophy of the deeper neck tissues.

During surgery it was noted further that the tissues did not bleed as much as in nonradiated patients.

Incisions were of the T type or its variations in all except one patient. In this one, a low collar incision was made. In the patient with the evident neck glands, block dissection was carried out in continuity with widefield laryngectomy. The remaining four patients underwent widefield laryngectomy alone.

Postoperatively three of these patients formed large pharyngostomas. One patient developed the pharyngeal opening because of unarrested cancer. However, the other two developed stomas as a result of late effects of irradiation upon their neck tissues.

A short resume of these latter two cases is given illustrating the problems encountered in their treatment:

CASE W.M., male, aged 58, received a tumor dose of x-ray therapy elsewhere in 1944 for squamous cell carcinoma of the left vocal cord. The patient was apparently well until 1949 when hoarseness recurred. Examination of the larynx showed a left cordal lesion, stage II, which was proven to be squamous cell carcinoma. In addition, the skin of the neck showed marked radiation changes; such as, atrophy, pigmentation and telangiectasia. Wide field laryngectomy was performed through a T incision on 3/14/49. A large pharyngostoma developed in the upper part of the incision a few days following surgery. Secondary suture of the pharyngostoma was done on 11/16/49 and it was not until six weeks later that the patient's neck tissues healed (Fig. 1). Follow-up examination of this patient was done in September 1958 and there was no evidence of
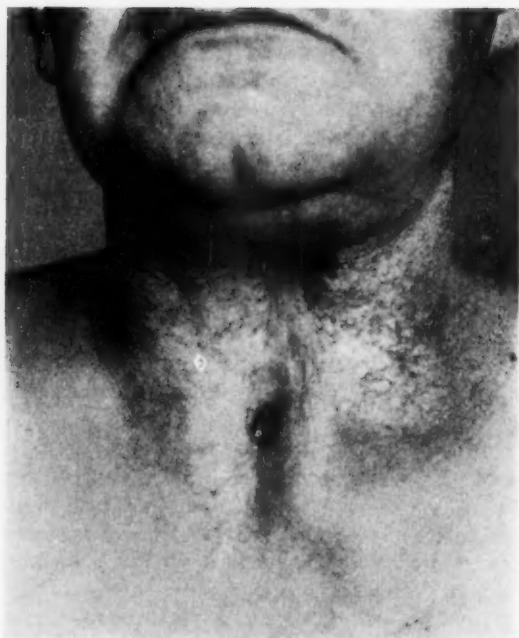
Fig. 1.—Case W.M., showing neck nine months after laryngectomy and six weeks after secondary suture of a pharyngostoma. Note the skin changes from irradiation five years previously for unarrested laryngeal cancer.

cancer; however, the tissues of the neck were board-like from further radiation reaction.

CASE H.M., aged 65, was treated elsewhere with x-ray therapy (6000 r) for a left supraglottic, stage II, squamous cell carcinoma in 1945. The patient was apparently well for 12 years and then developed a recurrence of the cancer in the same area of the larynx. On 4/8/57 a widefield laryngectomy was done through a low collar incision. A midline pharyngostoma developed. On 12/17/57 a full thickness sliding skin pedicle flap was created over the left side of the neck, the left supraclavicular and shoulder areas. On this date the flap was elevated and resutured to its bed. On 12/31/57 the mucosa surrounding the pharyngostoma was sutured and the pedicle flap was again elevated and advanced to cover the defect. Closure was accomplished without incident (Fig. 2).

Fig. 2.—Case H.M., showing neck six weeks after full thickness sliding pedicle graft was moved into place. Note radiation changes of the neck tissues about the graft. Patient had received x-ray therapy 12 years previously for laryngeal cancer. Laryngectomy was done because of recurrence.

These two cases illustrated two different methods used in closing pharyngostomas. In one case the closure was accomplished by secondary suture and in the other case by a full thickness sliding skin graft. It is important to note that in both cases there was enough redundant pharyngeal mucosa about the pharyngostoma so that it could be undermined, cut and trimmed for the first layer (lining) closure.

Disregarding the patient who died of cancer in this subgroup, the wounds in two patients healed per primam, while in the other two, special plastic procedures were necessary for the closure of persistent pharyngostomas.

Four of the patients are living and well five months to nine years following surgery and each one has learned esophageal speech.

Group II. Cancer controlled by x-ray therapy, in which cases, however, complications developed from irradiation.

1. *Early Complications Following X-ray Therapy*
Developed in Four Patients

In this subgroup, the patients' original laryngeal lesions were cordal stage I and were considered ideal for x-ray therapy. Apparently, the x-ray therapy arrested the cancer, but the patients continued to have general debility, weight loss, cough, dysphagia, and soreness of the throat. In each there was edema of the neck tissues, induration of the thyroid cartilages, and edema and redness of the laryngeal tissues. In addition to these above symptoms and signs, two of the patients showed ulceration and frank necrosis of the laryngeal tissues and ran a septic course. All four patients had varying degrees of stridor as well as evidences of recurrent tracheal aspirations from fixation of the laryngeal structures. Repeated biopsies were negative for cancer. In spite of adequate medical management, there was no improvement in the patients' general status or in the laryngeal symptoms and signs.

Widefield laryngectomy was performed in each case from three to ten months following the completion of the x-ray therapy.

The low collar incision was used in two cases. At the time of surgery their neck tissues showed moderate changes in the form of edema, inflammation and cartilage induration. Healing of the neck tissues was delayed in both patients. There was no sloughing of tissues although one had a persistent small fistula into the pharynx for a period of six months. Technically, the surgery was somewhat more difficult than had been experienced in patients in Group I, subgroup 1.

Since the other two cases required special surgical procedures, they will be discussed in more detail.

CASE E.T. This patient, aged 62, had x-ray therapy elsewhere for right cordal squamous cell carcinoma, stage I, in 1948. He became extremely ill following the x-ray therapy. He was unable to eat properly because of soreness of the throat, and lost weight rapidly. His course was septic and one of continuing debility. There was marked edema of the neck tissues and the laryngeal structures were beginning to slough internally. Medical measures were instituted, including transfusions, but they were of no avail in improving the patient's general or local condition. On 7/11/48 the larynx was removed as an emergency procedure. It was noted during surgery that there was a complete loss of normal tissue planes of the neck and the larynx was entirely necrotic. There was free pus in the deeper tissues of the neck. Only a partial closure of the wound was possible after the larynx was removed because of the severe local tissue reaction.
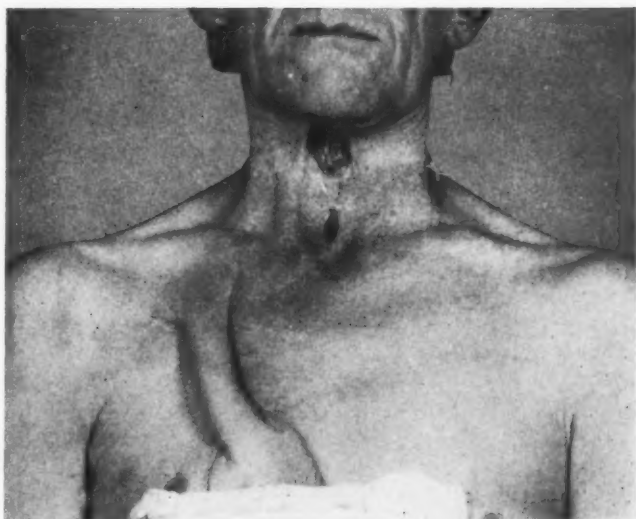
Fig. 3.—Case E.T., showing large pharyngostoma of neck 10 months after laryngectomy. Radiation changes of the patient's neck were severe and "early." Cancer was arrested and the larynx was removed because of radiation necrosis. The pedicle graft on the chest appears healthy but sloughed when an attempt was made to move it. This happened many times in this patient.

On the tenth postoperative day the patient developed a massive hemorrhage from the wound. The right lingual artery was ligated since it was found to be the source of bleeding. Following this the patient's septic course improved but due to a persistent pharyngostoma feeding was difficult. The tissues of the neck surrounding the pharyngostoma developed marked irradiation changes. The patient was taught to pass a feeding tube through the pharyngostoma for frequent feedings. In spite of this method and additional supplementary feedings, he remained undernourished.

Much difficulty was encountered in trying to close the pharyngostoma. On many occasions pedicle grafts of the chest, abdomen and neck sloughed without apparent cause (Fig. 3).

At no time could a healthy pedicle be moved in stages from the abdomen or chest. Due to lack of healthy tissues about the pharyngostoma, secondary suture failed also. Finally, a tube pedicle lined with a split thickness skin graft was moved in stages from the shoulder and neck for final closure.

Fig. 4.—Case E.T. (same patient Fig. 3), showing patient's neck healed. Note donor sites, right supraclavicular and shoulder areas. Twenty-eight plastic procedures during five years were required to close this patient's pharyngostoma.

In all, 28 plastic procedures were necessary during a period of five years before final closure was accomplished (Fig. 4). The patient is living and well at the present time and has developed an excellent esophageal voice.

CASE H.K., aged 58, completed x-ray therapy elsewhere for squamous cell carcinoma of the right vocal cord (stage I lesion) in December 1954. After completion of treatments, he developed severe soreness of the throat, dysphagia, stridor, general debility and weight loss. In fact, on occasion he had to be fed intravenously because his food intake was so limited. The patient's larynx was necrotic and there were marked irradiation skin changes of the neck. Biopsy showed no remaining cancer.

Because of the patient's general debility and the local tissue reactions, a laryngectomy was performed on 10/20/55. In addition to widefield laryngectomy, the severely damaged deep neck tissues and skin were removed en bloc with the larynx. Primary suture of the pharynx was done even though the constrictor muscles and submucosal tissues showed radiation reactions. In order to close the large surgical defect, a bipedicle full thickness sliding skin graft was created on the chest wall and moved up-

wards and sutured into place above the tracheal stoma. The donor site below the stoma was then closed by undercutting more healthy skin and subcutaneous tissues on the chest wall and sliding and suturing them into place.

The patient's postoperative course was uneventful and primary healing took place within 14 days. Later he ate well, gained weight, learned esophageal speech and has been in good health to date.

These four cases present some interesting data. In all, various degrees of perichondritis of the larynx developed following x-ray therapy. Although the cancer was controlled in each patient, perichondritis from the roentgen therapy was of such a severe nature that surgery was considered a lifesaving procedure. The surgery although somewhat difficult was more or less routine in two patients, while in the other two cases special operative techniques were used for tissue replacements.

Three of the patients are living and well from four to 11 years following surgery. The fourth patient died of cirrhosis of the liver complicated by a perinephritic abscess two years after laryngectomy.

2. *Late Complications Following X-ray Therapy Developed in One Patient*

CASE H.B. This patient received 6000 r of x-ray therapy elsewhere for squamous cell carcinoma of the larynx in 1940. The original description of the lesion shows it was apparently cordal in origin. The patient remained well until 1951 when he developed signs and symptoms of soreness, pain and dysphagia referable to the throat and larynx. In addition, he had developed severe radiation changes of the neck tissues. During 1951 he had several recurrences of throat symptoms which did not improve in spite of medical treatment. In March 1952 the tissues of the anterior part of the neck adjacent to the larynx ulcerated and sloughed.

In April 1952 the patient was admitted to the hospital. His neck showed external ulceration and sloughing of the thyroid cartilages (Fig. 5). Skin changes from late irradiation effects were severe. On palpation the larynx was board-like in character and appeared to be fixed to the surrounding neck tissues. There was a through and through fistula to the lumen of the larynx. There was no evidence of cancer as shown by repeated biopsy specimens. The patient's general condition was deteriorating because of his inability to take nourishment and because of repeated bouts of aspiration pneumonia.

On 5/12/52 an attempt was made to clean the sloughing wound by removing the necrotic laminae of the thyroid cartilage. This procedure did not improve the patient's general or local condition (Fig. 6). On 7/22/52 a laryngectomy and excision of the involved neck and skin tissues
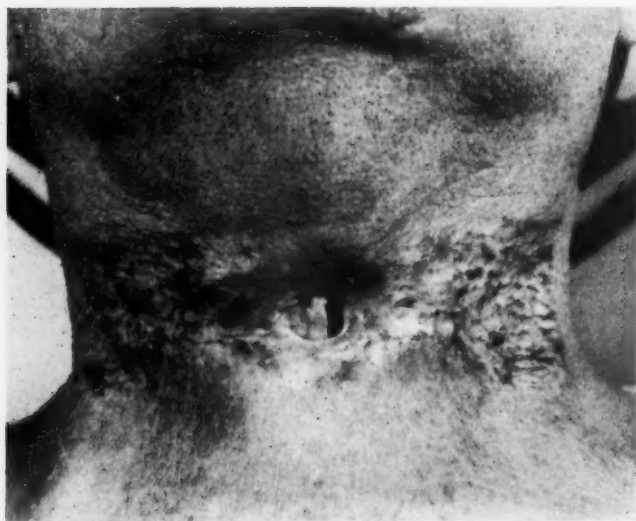
Fig. 5.—Case H.B., showing neck tissues 12 years after x-ray therapy for laryngeal cancer. Note through and through ulcer and necrotic thyroid cartilage laminae. Atrophy, telangiectasia and pigmentation of the surrounding tissues were severe.

were done in continuity. The pharyngeal tissues were closed by primary suture. In order to close the denuded area above the tracheal stoma, a large bipedicle sliding full thickness skin graft was created on the chest wall, moved to this area and sutured in place to tissues undamaged by irradiation. The newly created surgical defect on the chest wall below the tracheal stoma was covered by a split thickness skin graft taken from the abdomen (Fig. 7).

The patient's tissues healed per primam except for a small sinus tract beneath the upper sliding graft (Fig. 8). His general condition improved and he developed a mediocre esophageal voice. In 1956 he died, reportedly from "heart trouble."

This patient illustrates a severe late complication following x-ray therapy. There was no evidence of cancer either from biopsy specimens or from examination of the tissues removed at the time of definitive surgery.

Fig. 6.—Case H.B. (same patient Fig. 5), showing neck after necrotic thyroid cartilage laminae were removed.

This was the first case encountered in the whole series of patients where it was found necessary to excise severely damaged irradiated tissues along with the larynx, and to replace the denuded areas by a sliding bipedicle graft and a split thickness graft in a one-stage surgical procedure. (The same surgical techniques were used with modifications in case H.K., Group II, subgroup 1.) This one-stage operation is undoubtedly the surgical procedure of choice in such cases since it is designed to replace damaged tissues by immediate grafting.

Pharyngeal Cancer

Group III. There were three patients in this group. One patient had primary squamous cell carcinoma of the posterior left lateral oropharyngeal wall, while the other two had primary squamous cell carcinomas of the right lateral pharyngeal wall extending to the homolateral vallecula. One case had palpable lymph nodes in the
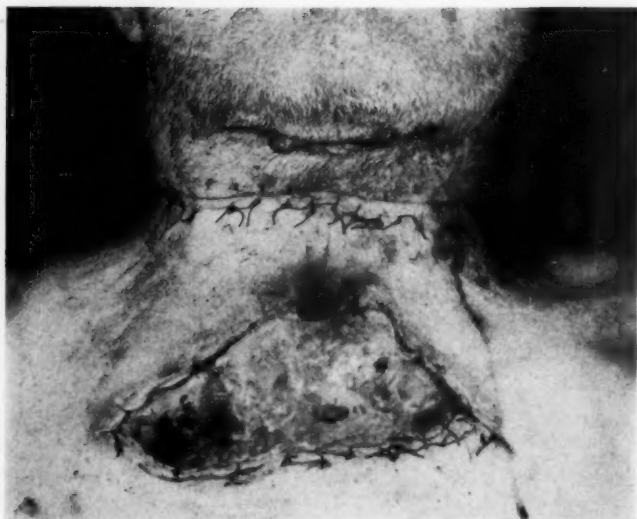
Fig. 7.—Case H.B. (same patient Fig. 5), showing neck after laryn-
gectomy and plastic repair. Note position of bipedicle sliding graft above
tracheal stoma. It covers the sutured pharynx and fills in the large excisional
defect. The donor area has been covered by a split thickness skin graft
taken from the abdomen. The donor area can be closed by further under-
cutting and moving the skin and subcutaneous layers on the chest wall up-
wards, as was done in a subsequent case H.K. (Group II, subgroup 1).

right cervical digastric area on initial examination. X-ray therapy
was recommended for the treatment of the primary lesion in each
patient as the initial form of therapy.

The patients in this group are discussed briefly to show that in
some instances x-ray therapy may convert an inoperable neoplasm
into one of operability. In only one of the patients with necrosis of
the mandible could the surgical procedures be considered as being
complicated by the irradiation.

The case histories of the following two patients are cited to show
the types of surgical procedures carried out following radiation ther-
apy.

Fig. 8.—Case H.B. (same patient Fig. 5), showing that the neck has healed. Note that all the severely damaged radiated areas have been replaced with viable healthy grafts.

CASE E.K. The primary lesion was diagnosed as squamous cell carcinoma of the posterior and lateral oropharyngeal walls. No nodes were palpable on the left side of the neck on initial examination. In 1955, 6055 r of x-ray therapy was delivered to the area. The primary lesion appeared to be controlled immediately, but four months later nodes appeared in the left side of the neck and there was an ulcerated area at the former pharyngeal primary site. This proved to be squamous cell carcinoma by biopsy.

A partial pharyngectomy and left block dissection of the neck were done on 8/9/55. The tissues healed. However, necrosis of the left side of the mandible occurred and a fistulous tract developed into the floor of the mouth late in 1957.

In February 1958, a left hemimandibulectomy was performed and the tissues about the fistula were excised. No neoplasm was found in the microscopic sections of these tissues. A sliding pedicle graft was created on the patient's neck posteriorly which was to be lined with a split thickness skin graft and swung anteriorly to close the fistula. However, the patient suddenly expired on 10/2/58 following thrombosis of the left internal carotid artery. No residual cancer was found at postmortem examination.

CASE E.A. The patient had an undifferentiated primary squamous cell carcinoma of the right pharyngeal wall and vallecula which was treated with 4600 r of x-ray therapy in 1951. In 1953, 4500 r were again delivered to the neck. In addition 1500 r were given from a cobalt bomb source which was placed in the patient's pharynx during anesthesia. Following this therapy, the patient did well until 1955 when he had a recurrence of the primary neoplasm at the tip of the epiglottis.

Accordingly, on 6/7/55 a transhyoid epiglottectomy and partial removal of the base of the tongue were done. An interesting sidelight in this case is that this patient could not eat without aspirating foods following the above surgical procedure and had to take nourishment by gavaging, a procedure he did himself. Therefore, on 3/11/58 a narrow field laryngectomy was performed.

This patient has lived for eight years and is now apparently free from cancer. His general health is poor at present probably due to the fact that he has developed muscular atonia of the esophagus.

The third patient in this group died of distant metastases. The primary site of the cancer was the right lateral pharyngeal wall which proved to be a highly undifferentiated squamous cell carcinoma upon biopsy and microscopic tissue examination. The primary lesion was apparently controlled by x-ray therapy which was delivered in 1955. He is discussed in this group because a block dissection of the right side of the neck was done for palpable nodes on 3/8/56. His neck tissues healed slowly but adequately. He expired two years following x-ray therapy.

As noted above, surgical experiences in this group of cases varied. The technical problems of the surgery itself were not remarkable. Healing of the tissues was not unduly delayed in two cases, while in the third case the necrotic mandible and mouth fistula presented special problems. Time intervals following completion of the x-ray therapy and surgical intervention varied from five months to five years. No special problems concerning the larynx were present since the primary neoplasm was anatomically distant from it and since the radiation therapy did not involve it.

SUMMARY

Twenty-two cases with primary squamous cell carcinoma of the larynx and pharynx have been discussed. All patients had x-ray therapy as the initial treatment. In all patients surgery was performed, varying from two months to 12 years, subsequently.

The laryngeal cases were presented in subgroups "early" and "late." Some of the "early" cases showed severe x-ray reactions and were the most difficult to treat surgically.

For convenience in presentation, the cases in Group III were not divided into subgroups.

The greater number of patients in the "early" subgroups did not present special surgical and healing problems except in two instances, E.T. and H.K. (Group II, subgroup 1). However, in patients in the "late" subgroups the problems were multiplied. The outstanding surgical difficulties were the closing of pharyngostomas and the replacement of tissues damaged by irradiation. In various patients the methods used were as follows:

1. *Secondary Suture of the Pharyngostoma.* This was accomplished when there was adequate mucosa and submucosa of the pharynx for the first layer closure and enough healthy skin and subcutaneous tissue for final closure.

2. *Closure by a Delayed Single Pedicle Sliding Full Thickness Skin Graft.* Likewise, in this procedure there must be sufficient healthy mucosal and submucosal tissues for the first layer closure so that the unlined pedicle may be used to cover the outer raw submucosal surfaces.

3. *Distant Pedicle Grafts.* Distant pedicle grafts with proper undersurface lining must be used in other cases when the pharyngostoma is so large that there is no mucosal or submucosal layer to use in the closure. The pedicles must be developed from skin layers of the chest wall, abdomen, neck or shoulder and moved in stages for closure. Such techniques are often complicated in these patients since their tissues heal poorly due to continued malnutrition.

4. *Bipedicle Full Thickness Sliding Skin Grafts.* Bipedicle full thickness sliding skin grafts were created in two patients to close surgical defects. In both cases the procedure was carried out in one-stage operation with laryngectomy, thus eliminating longer periods of hospitalization and morbidity. In both cases the pharynx was closed without fistula formation even though the tissues showed radiation effects. In one, the donor site on the upper chest was covered by a split thickness graft while in the other full thickness skin was undermined and moved into position for closure.

CONCLUSIONS

1. Surgery of the neck in patients following x-ray therapy for unarrested primary squamous cell carcinoma of the larynx can usually be done within the first year following radiation therapy without surgical technical difficulties and without undue complications in healing.

2. There are exceptional cases, however, with "early" radiation changes that may present many problems, not only in the performance of the surgery but in healing. Some of the patients in this series had varying degrees of perichondritis of the laryngeal cartilages and were seriously ill in spite of apparent arrested cancer.

3. Surgery of the neck on patients who have been irradiated 12 months or more previously for cancer of the larynx is fraught with many difficulties. The surgeon experiences these during the performance of the surgery and during the postoperative care of the patient. This is true whether there is persistent cancer or not in these patients.

4. When x-ray therapy is used to control primary cancer of the pharynx in patients with inoperable disease, surgery may be possible later in some of these cases. The surgical procedures will be varied.

384 Post Street

XXXI

THE DIAGNOSIS OF
CHRONIC INFLAMMATORY LESIONS
OF THE SPHENOID SINUS

J. H. MAXWELL, M.D.

B. JAY HILL, M.D.
(by invitation)

ANN ARBOR, MICH.

The diagnosis of chronic inflammatory lesions of the sphenoid poses problems not encountered in chronic infections in the other paranasal sinuses. The first problem, often incapable of easy solution, is the localization of the lesion to the sphenoid sinus on the basis of symptoms and physical findings. The second problem is the differential clinical diagnosis to determine whether the lesion is inflammatory or neoplastic, and whether the disease is primary in the sphenoid sinus or whether the sphenoid block has been invaded secondarily.

The purpose of this paper is to emphasize the obscurity of chronic inflammatory lesions of the sphenoid, and by means of case presentations to demonstrate some of the differential diagnostic procedures, particularly radiographic, which may be required prior to definitive surgical therapy.

Certainly this is not a new subject. The difficult problems peculiar to the sphenoid have been recognized for many years. Proetz[1] outlined these well when he summarized the particular anatomical and physiological features of the sinus and commented on its 13 important and vulnerable neighbors. Proetz also remarked on the obscurity of chronic sphenoid infections and stated that they rarely disturb the neighboring nerves and vessels but when they do, the symptoms tend to be referred to those structures rather than to the

sphenoid itself. The role played by the sphenoid sinus in vague but harassing headache in a patient with signs of low-grade chronic infection may be extremely difficult to evaluate. In discussing this paper of Proetz, Van Alyea[2] made the following pertinent statement. "Every year or two the sphenoid sinus is taken out of obscurity, given an airing, then returned to its normal role as the most neglected of the nasal sinuses." Van Alyea warned that one must develop the habit of suspecting and investigating the sphenoid in cases of deep seated headache of undetermined etiology. The importance of a detailed history in cases of headache due to sphenoid sinus infection was stressed by Canfield.[3]

Although no attempt will be made in this presentation to review the voluminous literature describing the sphenoid sinus and its diseases, I wish to commend for your re-reading the paper by our own President, Dr. Fred Dixon,[1] and that by Dr. Austin T. Smith,[5] both of which were presented at the annual meeting of this Association last May. The variable anatomical forms of the sphenoid were studied and presented in detail by Van Alyea.[6] The excellent treatise on the intracranial complications of sphenoiditis by Teed[7] has an exhaustive and valuable bibliography. The paper presented by Dr. Oscar Hirsch[8] at the Sixth International Congress of Otolaryngology describes various pathological processes which may involve the sphenoid, and recommends the transeptal approach to the cavity.

It is generally conceded that the sphenoid sinus is the least accessible of all sinuses to injury and infection and that a serious fulminating acute sphenoiditis is rather rare. Likewise, the sphenoid is the least accessible of all the paranasal sinuses to the surgeon. And this is fortunate; for if it had been subjected to the frequent and promiscuous needlings, washings, punctures, and other insults which have been inflicted on the maxillary antrum, it, along with its thirteen influential neighbors, would have accounted for more than their share of intracranial suppurations. Hirsch[8] stated that "caution in exploration of this sinus still persists in spite of the ease of present day methods." If this "caution" were only heedfulness and prudence in regard to danger it would be wholesome and should be applied to operations on the antrum and ethmoid, in fact, to all surgical procedures. However, such caution expressing apprehension and even fear places the sphenoid out of sight and out of mind keeping it in its accustomed place of neglect.

Inflammatory disease limited to the sphenoid or the sphenoid and posterior ethmoid cells alone is rare; and those closed lesions such as mucoceles or pyoceles are extremely rare. The symptomatology is vague and the diagnosis difficult. Misdiagnosis and faulty treatment such as reported by Cody,[9] Neffson,[10] and Anthony and Williams,[11] in these obscure cases has been recorded frequently enough to make one wonder if isolated chronic sphenoiditis is so rare as has been reported. Simon and Tingwald[12] commented that the diagnosis of sphenoid mucocele was usually made at autopsy or during an ill-advised intracranial operation. Linthicum et al[13] in 1946 found 25 cases of sphenoid mucocele reported. Pendergrass, Schaeffer, and Hodes[14] state that about 50 cases of sphenoidal mucoceles, including those discovered at autopsy, have been reported.

The one important symptom noted in the cases to be presented here is headache. Most frequently it has been bifrontal and temporoparietal. A deep seated pain behind the eyes has been noted frequently and in the more severe suppurative processes in this series pain was occipital. Deep seated chronic nagging headache should prompt careful investigation of the posterior group of sinuses. Too frequently such a headache is attributed to a tension state. In a case of isolated sphenoid suppuration, it is unusual to find evidence of disease on anterior rhinoscopy. If there is a wide olfactory fissure, a small middle turbinate, and a favorably deviated septum, pus may be seen in the region of the sphenoidal ostium providing there is an opportunity for drainage. Careful nasopharyngeal examination is mandatory. Except in rare instances, such as the cases in this series, numbers 4, 5, and 6, pus, granulation tissue, or edematous mucous membrane should be visualized in the spheno-ethmoidal recess.

Next and most important is the radiographic examination. Lateral and submentovertical views in stereo must be evaluated carefully. Simple inflammatory lesions produce increased density in the sinus and in some instances it is possible to see a fluid level. If sclerosis and evidence of proliferation of bone in the walls of the sinuses are demonstrated, it almost certainly means chronic inflammatory change. In no instance have I seen sclerosis of bone around an expanding or infiltrating neoplasm in the sinuses. If destruction of bone is noted on the x-ray film, a wide variety of lesions in and about the sphenoid must be considered in an effort to determine if the lesion is inflammatory or neoplastic and if the sphenoid sinus is the primary seat of the
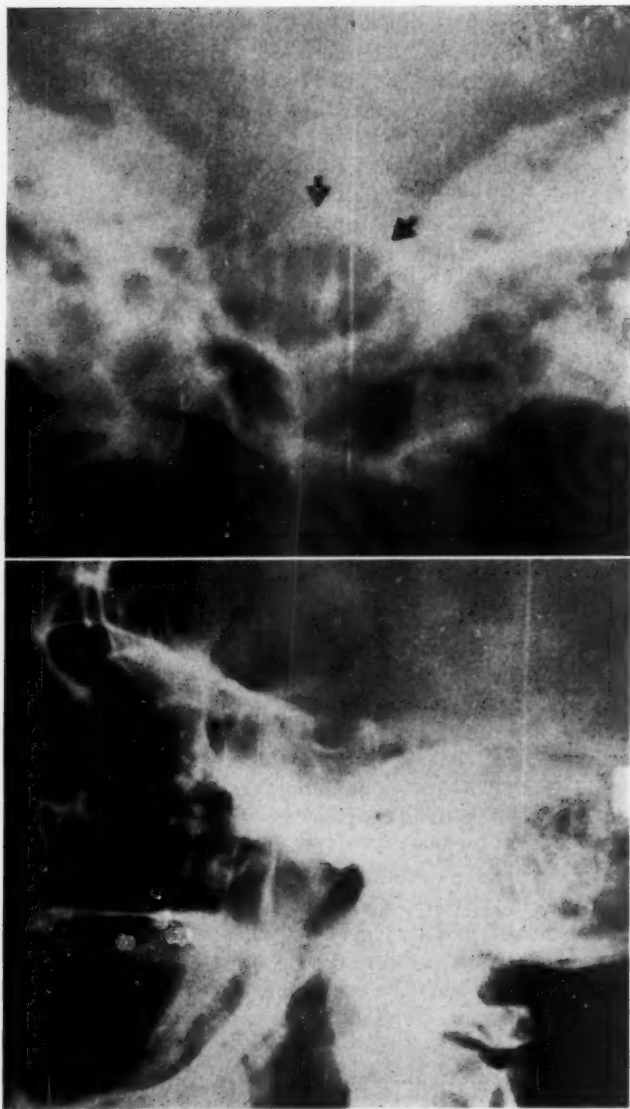
Fig. 1.—Case 1. G.F. UH 650910 Sclerosing right sphenoiditis. Lateral view shows diffuse density of the sphenoid sinuses. Granger view shows sclerosis and thickening of the roof and lateral walls of the sphenoid sinus (arrows).

lesion. Differentiation must be made among suprasellar erosion, intrasellar erosion, parasellar erosion, and primary involvement of the sphenoid sinus or the clivus. Also in such a case, the possibility of sphenoid invasion secondary to nasopharyngeal neoplasm always must be borne in mind. In selected cases, particularly when neoplasm is suspected or where there seems to be parasellar erosion, arteriograms and planograms may be of diagnostic value.

The case reports to be presented will be in four groups. In group I, there are three cases of relatively obscure isolated sphenoiditis with diagnostic objective findings which should have permitted earlier diagnosis. In group II are three cases of sphenoid mucocele. Two of these patients had normal findings regarding the nose, nasopharynx, eyes, and cranial nerves. One had an orbital apex syndrome or sphenoid fissure syndrome associated with an extensive mucocele involving all the ethmoids and sphenoid on one side. In group III are two cases of unusual inflammatory disease which are not understood clearly at this time. Group IV consists of several cases of neoplastic disease invading the sphenoid sinus which are presented in an effort to emphasize the importance of complete and careful history and examination and the necessity of highly critical evaluation of the radiographs.

REPORT OF CASES

GROUP I

CASES OF ISOLATED CHRONIC SUPPURATIVE SPHENOIDITIS

CASE 1. G. F. UH 650910. This patient, a white male, aged 55, was admitted on the Neurology Service on December 1, 1948 complaining that for three months he had had attacks of severe bilateral frontal headache occurring almost any time during the day and lasting for about four hours. As the pain became more severe, it seemed to be localized deep in the right temple also. The onset of the headache was usually sudden and its disappearance gradual. The patient had no other complaints and stated that he felt well between attacks. Since there was no neurological deficit, the patient was referred to the Department of Otolaryngology where the only additional item in the history was that during the headache the patient

Fig. 2.—Case 2. R.K. UH 886266 Bilateral sclerotic sphenoiditis. P.A. view shows the extreme sclerosis and thickening of the roof and lateral walls of the sphenoid sinuses (arrows). Lateral view shows the sclerotic roof of the sphenoid sinus corresponding to the floor and anterior wall of the sella turcica.

had some feeling of obstruction on the right side of his nose and also lacrimation of the right eye.

Examination revealed a very small pea-sized edematous polyp in the region of the natural ostium of the sphenoid on the right side. There was no associated purulent discharge.

Roentgenograms of the paranasal sinuses showed diffuse clouding of the right sphenoid sinus with some sclerosis of its walls. This is shown to best advantage on the Granger view involving the roof and lateral wall (Fig. 1).

Under local anesthesia, the small polyp was grasped with a forceps and evulsed. There was an immediate profuse discharge of thick yellow pus from the sphenoid ostium. On microscopic examination, the polyp showed active chronic purulent productive sinusitis and no neoplasm.

The patient's symptoms returned promptly and on December 22, 1948, a submucous resection of the septum and removal of the anterior wall of the right sphenoid sinus were performed. Pus and polypoid tissue were found in the sphenoid sinus. The patient was relieved of his headache.

CASE 2. R. K. UH 886266. This patient, a white male, aged 55, was admitted on the Otology Service on November 7, 1957. He complained of constant and continuous headache of eight weeks' duration. The onset was apparently rather sudden and not associated with symptoms suggesting a severe upper respiratory infection. The pain was in the bilateral frontal area, seemed to be in back of both eyes, and tended to extend to the occipital region. At first the pain was worse on the right side but it was bilateral at the time of examination. The only other symptoms were lassitude, and the occasional sensation of foul tasting material in the throat at night. There had been no visual difficulties. Four weeks prior to the time of this examination the patient had been hospitalized for a week. At that time roentgenograms of the skull were reported as "negative." He had been taking chloromycetin for a month.

On examination it was noted that there was a little pus in the right lateral angle of the nasopharynx apparently coming from the
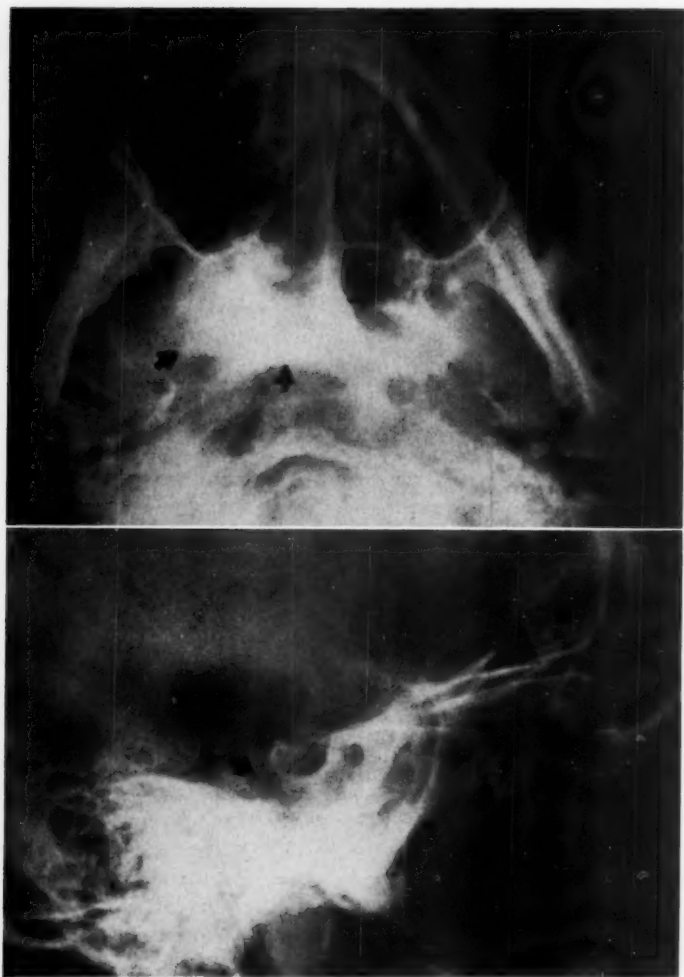
Fig. 3.—Case 3.   R.W.   UH 637092   Sclerotic osteitis of the sphenoid sinus with dehiscence posteriorly and epidural abscess.   Base view shows sclerotic thickening of the walls of the right sphenoid sinus and the interspherenoidal septum (arrows).   Lateral view shows diffuse sclerotic density over the sphenoid sinuses.   Note the large defect in the clivus posteriorly (arrow).

region of the spheno-ethmoidal recess.   The temperature and white blood cell count were normal.   There was no neurological deficit.

Roentgenograms of the skull showed pronounced sclerosis of the roof and lateral walls of the sphenoid sinus.   The septum between the two sphenoid sinuses was not identified.   The sclerotic bone appeared to be unusually thick along the anterior wall of the right sphenoid (Fig. 2).

On November 12, 1957 an external frontal, ethmoid, and sphenoid exenteration was done.   The entire ethmoidal labyrinth appeared to be normal but there was some necrotic bone in the region of the natural ostium of the right sphenoid.   On removing the anterior wall of the right sphenoid, it was seen that the sinus was large and extended across the midline.   It was lined with markedly thickened mucous membrane and contained thick pus.   The left sphenoid was opened and found to be very small and rather anteriorly situated.   It showed no evidence of disease.

The histological slides demonstrated purulent exudate and fragments of nasal respiratory epithelium showing acute and chronic inflammation.   There were clumps of mycelia which seemed to be compatible with Candida albicans or actinomycosis.   These were not identified positively.

After operation, the patient was relieved of his symptoms.

CASE 3.   R. W.   UH 637092 . This patient, a white male, aged 34, was admitted on the Neurology Service, April 28, 1948, complaining of right-sided headaches which had been present intermittently since 1942.   The headache usually started in the right occipital region and radiated over the right temple to the right frontal region and therefore became generalized over the right side of the head.   These usually started at night and would last about two days after which he might be symptom free for as long as one or two months.   For five weeks prior to admission, the pain had been constant over the right side of the head and deep in back of the right eye.

After repeated examinations, a small stream of pus was noted in the lateral angle of the nasopharynx, apparently coming from the region of the right spheno-ethmoidal recess.

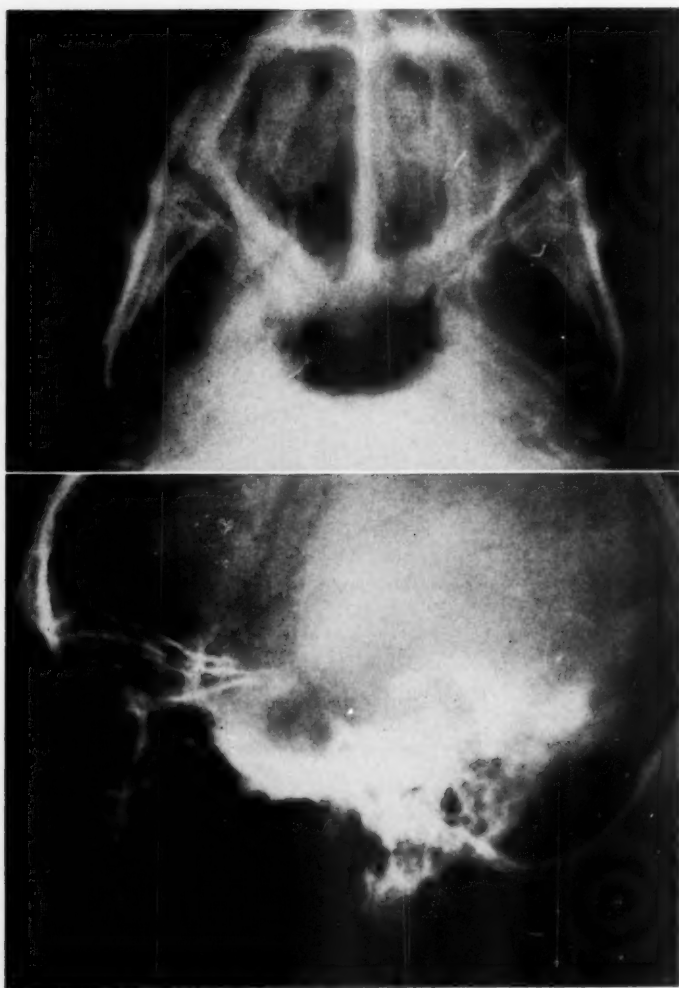Fig. 4.—Case 4. F.K. UH 602279 Mucocele of the right ethmoid sinus extending posteriorly to involve the sphenoid sinuses. Lateral view shows extensive bone destruction involving the floor of the sella and the sphenoid sinuses. Base view is underexposed and demonstrates the sphenoid area poorly but does show benign expansile lesion in the right ethmoid sinus (arrow).

Roentgenograms of the skull and paranasal sinuses showed diffuse sclerosis over the sphenoid sinuses in lateral projection. There was destruction of the clivus immediately behind the sphenoid sinuses. The base view revealed the abnormality to be confined to the right sphenoid area. The pronounced sclerosis involved all of the walls of the right sphenoid including the septum and extended laterally beyond the anticipated confines of the sinus. Destruction of the clivus was seen directly posterior to the right sphenoid and extended just across the midline. There was a precise and slightly dense margin at the edge of the destroyed portion of the clivus (Fig. 3).

On June 2, 1948, a submucous resection of the nasal septum and right sphenoidotomy were done. The sphenoidal ostium was occluded by what appeared to be a fibrous granular polyp. This polyp was removed and an attempt was made to enlarge the natural ostium but the surgeon found that the wall was very thick and sclerotic and he was not successful in making a large opening into the sinus. The patient's headaches were relieved completely, however, and he was discharged from the hospital on June 4.

He was re-admitted on June 28 because continuous severe headache had recurred and double vision had developed suddenly on June 20. Examination again revealed pus coming from the right sphenoid. There was paralysis of the lateral rectus muscle on the right. The white blood count was 14,000. Lumbar tap showed normal spinal fluid. There was no neurological deficit other than the lateral rectus paralysis.

On July 2, 1948, a right external ethmoid and sphenoid exenteration was performed. There was slight thickening of the lining of the posterior ethmoids. Granulation tissue was seen occluding the ostium of the right sphenoid sinus. After removing the anterior wall of the sphenoid sinus, granulation tissue was visualized at the base of the intersphenoidal septum. On removing this granulation tissue, there was an exudation of thick pus. The postero-inferior wall of the sphenoid sinus was greatly thickened and obviously the seat of an osteomyelitis. On removing this, an epidural abscess was encountered. It was possible to drop a probe into the abscess cavity for a depth of about two centimeters. After operation, there was very prompt relief of the headache and the patient was discharged from the hospital on July 10, 1948.

Fig. 5.—Case 5. J.D. UH 904656 Mucocele involving both sphenoid sinuses. Lateral view shows smoothly rounded walls of the sphenoid sinus anteriorly and inferiorly. Sellar floor, dorsum sellae, and superior clivus are eroded. Base view shows posterior border of the hard palate projected over the sinus cavity (vertical arrow), erosion of the clivus (oblique arrow) and apparent expansile erosion into the left pterygoid fossa (horizontal arrow).

The patient's headaches recurred on July 14, 1948, and he was re-admitted to the hospital. A cannula was inserted into the sphenoid sinus and suction applied which relieved the pain promptly. He was placed in prone position for ten hours out of each twenty-four to facilitate drainage and he soon became asymptomatic and afebrile. He was discharged from the hospital on August 2, 1948, and continued to be symptom free.

GROUP II

THREE CASES OF SPHENOID MUCOCELE

CASE 4. F. K. UH 602279. This patient, a white male, aged 70, was admitted to the Department of Ophthalmology on October 23, 1946, complaining of blindness in his left eye and prominence of the right eye. In the patient's history, it was noted that diplopia had developed eight years previously but this had been corrected with glasses. There had been excessive lacrimation of the right eye for four years and a noticeable swelling above the inner canthus of the right eye for two years which seemed to remain the same size and was never painful. A month prior to examination, the patient had developed severe bilateral frontal headache and had suddenly lost vision in his *left* eye.

Ophthalmological examination demonstrated a right proptosis with downward displacement of five millimeters and outward displacement of five millimeters. A hard mass was palpable in the upper, inner portion of the right orbit. The vision in the right eye was 6/9 plus 2 and there was complete loss of vision even to light perception in the left eye. The right fundus was normal but the left fundus showed slight temporal pallor of the disc. There was no paralysis of the extra-ocular muscles.

In the Department of Otolaryngology it was noted that there was slight polypoid hyperplasia of the mucous membrane in the right middle meatus of the nose. The left side of the nose appeared to be normal. Mirror examination of the nasopharynx showed a thin stream of mucopurulent exudate coming over the posterior end of the right inferior turbinate. The mucous membrane in the region of the right spheno-ethmoidal recess appeared to be edematous and hyper-

Fig. 6.—Case 6. R.F. UH 863728 Pyocele of the right sphenoid sinus. Lateral view shows erosion of the floor of the sella and of the clivus. Base view shows the walls of the sphenoid sinus intact. The right sphenoid sinus is much larger than the left (asymmetry is common but this is extreme in degree) but nevertheless is much more dense than any other paranasal sinus. Note posterior wall coursing obliquely across clivus (arrows).

plastic. The mass in the upper, inner angle of the right orbit seemed to have a rather rubbery consistency.

Complete neurological examination added no further information.

X-ray examination of the sinuses and skull showed under development and thickened mucosal lining of both antra. The frontal sinuses were absent. Soft tissue density was noted in the region of the right orbit whose medial bony margin was irregular and lacking in definition. Lateral projection of the skull showed extensive bone destruction involving the floor of the sella. There was demineralization of the clinoids, the dorsum sellae, and the clivus. The submento-vertical projection showed diffuse density in the region of the right lateral wall of the sphenoid sinus with extension of the diffuse density into the region of the posterior ethmoids on the right (Fig. 4).

On November 15, 1946, a right external ethmoid and sphenoid exenteration was performed. A large mucocele was encountered which involved the entire right ethmoidal labyrinth and both sphenoids which had been converted into one cavity. The patient's post-operative convalescence was uneventful and he regained some, although not useful vision in the left eye.

CASE 5. J. D. UH 904656. This patient, a colored female, aged 52, was admitted on the Neurology Service on September 28, 1958, complaining of severe pain over the entire left side of her head. She stated that she had been well until early in 1958 when she first noted pain deep in the region of the left eye. Later, the pain involved the frontal region and then spread to the parietal and occipital areas. The pain was described as a continuous and constant aching which kept her awake at night. A month prior to this examination she had experienced a vomiting spell which lasted two or three days and during that time she developed diplopia.

The neurological examination showed no abnormality other than evidence of a partial third nerve paralysis as indicated by a ptosis of the left lid. On general physical examination, it was found that the patient had diabetes mellitus. She was afebrile and the blood count was normal. Ophthalmological examination revealed a mild diabetic retinopathy and what was concluded to be a pseudoptosis.
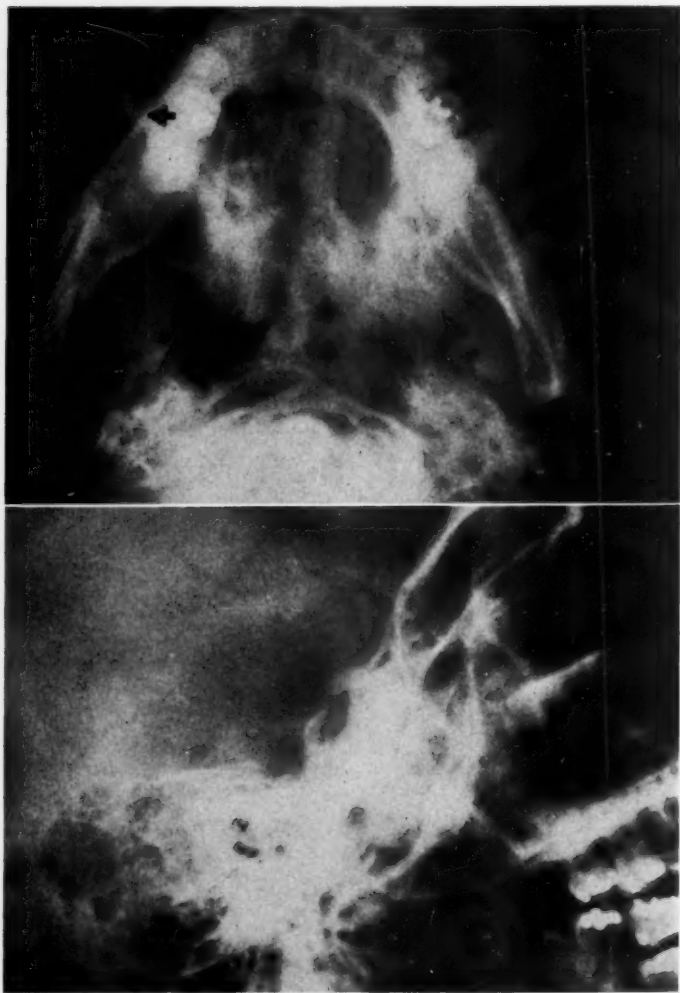
Fig. 7.—Case 7.   B.B.   UH 914077   Lethal midline granuloma with pansinusitis and osteitis of sinus walls.   Lateral view shows sclerosis of the frontal and sphenoid sinuses.   Base view shows sclerotic thickening of the lateral walls of the maxillary antra (upper horizontal arrows) and of the sphenoid sinuses including the septum (lower arrows show thickness of posterior wall).

In the Department of Otolaryngology the pharynx, nose, and nasopharynx appeared to be entirely normal. There was no clinical evidence of paranasal sinus disease.

Routine and base views of the skull showed erosion of the floor of the sella, the entire dorsum sellae, and the upper clivus which had precise and slightly dense margins. The lateral walls of the sphenoid sinuses were not identified in their usual location and the intersinal septum appeared to be absent. The erosion appeared to extend into the pterygoid fossa bilaterally (Fig. 5). Bilateral carotid angiograms excluded aneurism. Angiography was done because there was some calcification in the parasellar region which might have been compatible with calcification in the wall of an aneurism.

After the patient's diabetes was brought under control, a left external frontal-ethmoid-sphenoid exenteration was performed on August 13, 1958. The frontal sinus, the anterior, and the middle ethmoid sinuses appeared to be quite normal but there was a little thickening of the lining of the extreme posterior ethmoids. The thin anterior wall of the sphenoid sinus was bulging anteriorly. On opening the sphenoid sinus an enormous mucocele was encountered which contained thick mucoid, glistening material. After removing the rostrum of the sphenoid, the anterior walls of both sphenoid sinuses were resected. These constituted one large cavity with thick-ened edematous mucosal lining. After the removal of this lining a 3 x 2 cm dehiscence was noted in the posterosuperior wall of the sphenoid which exposed the dura over the pituitary and upper portion of the pons. The retro-orbital portion of the optic nerve lay exposed in the lateral aspect of the left sphenoid.

The pathology report indicated respiratory mucous membranes showing marked edema and infiltration by plasma cells and lympho-cytes. In some areas deposits of cholesterol, chronic inflammatory cells, and fibrosis were seen. There was no evidence of neoplasm.

The patient had an uneventful postoperative course without any visual difficulty. She experienced complete relief from her pain.

Case 6. R. F. UH 863728. This patient, a white female, aged 64, was admitted on the Neurology Service on March 19, 1957. She stated that on the morning of January 10, 1957, she awakened with
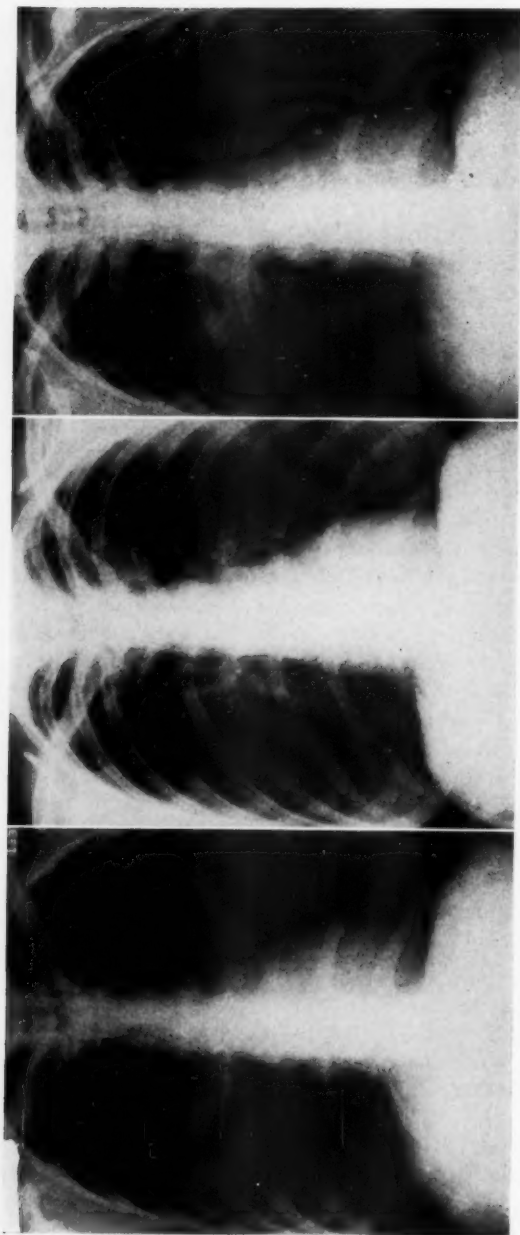
Fig. 8.—Case 7. B.B. UH 914077 Lethal midline granuloma with pansinusitis and sclerosing osteitis. (a) Negative chest.
(b) Nodular lesion in right upper lung 2 months later. (c) Rapid growth and excavation during next one and one-half months.

severe occipital headache which radiated to both temporal areas and lasted about two hours. Since that time similar episodes had occurred almost daily, lasting for longer periods and being of increasing severity. These headaches practically always occurred before breakfast and were preceded by profuse sweating and a feeling of weakness. The patient stated that sometimes the pain extended to the frontal region on both sides. She obtained no relief with medication which included narcotics. Prior to January 10, the patient had had occasional headaches which had been diagnosed as migraine. Two years previously she was hospitalized for a two week period during which time she had considerable occipital headache but her diagnosis at that time was said to have been a "nervous breakdown."

A complete neurological examination failed to reveal any evidence of pathologic change, except increased spinal fluid pressure and total proteins of 42 milligrams per cent. Electroencephalogram, glucose tolerance test, and examination of the ocular fundi and fields were normal.

In the Department of Otolaryngology, objective examination of the nose, nasopharynx, ears, and pharynx showed no abnormality. There was no clinical evidence of paranasal sinus disease.

Roentgenograms of the skull with base views showed destruction of the floor of the sella turcica and of the clivus in its superior aspect. Lack of erosion of the anterior aspect of the base of the dorsum sella tended to indicate that the destructive lesion was not of intrasellar origin. The base views showed a very large right sphenoid sinus which had a much greater density than the small left sphenoid. The walls of the sphenoid sinuses appeared to be intact (Fig. 6). Laminagraphy contributed no further information.

After reviewing the x-rays and various clinical examinations, it was felt that the patient probably had a sphenoidal mucocele. On April 10, 1957, a submucous resection of the nasal septum and a trans-septal sphenoidotomy were done under local anesthesia. The bone of the anterior face of the sphenoid was eburnated and unusually thick, measuring nearly 4 mm. With considerable difficulty, the anterior wall of this right sphenoid was perforated with a chisel and then the opening gradually enlarged with chisel and Kerrison rongeur. A considerable area of the anterior face of the sphenoid was removed
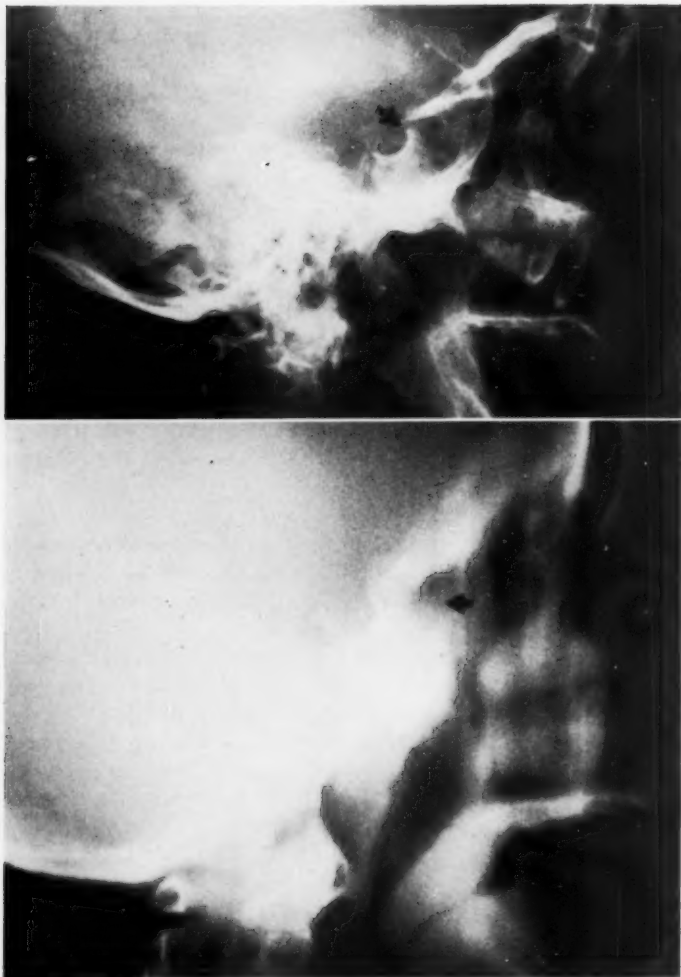
Fig. 9.—Case 8. C.J. UH 893900 Plasmocytic granuloma (not neo-plasm) of the left sphenoid and posterior ethmoid sinuses. Lateral view shows apparent defect in the anterior wall of the sella turcica (arrow). Laminagram just off the midline does not demonstrate the sellar dehiscence but does show a large defect in the anterior wall of the sphenoid sinus (arrow) not appreciated on routine films. Note the sclerotic walls favoring inflammatory etiology.

without exposing the cavity of the sinus. Beneath the thickened bony wall was a firm membrane which, on inspection, suggested dura mater. On rechecking the x-rays it was obvious that it must be sphenoid lining. This was incised and a pulsating, yellow, purulent discharge was released. After extensive removal of the anterior face of the sphenoid, some thick, creamy exudate was aspirated. Some of the contents of the sphenoid consisted of thick and inspissated material which required removal with a curet. When the cavity was empty, the posterior wall of the sphenoid sinus was seen to be pulsating. Removal of the lining posteriorly exposed dura of the mid brain. The pulsation of the vertebral artery was seen clearly on the right side.

Material removed from the sphenoid sinus was shown to consist of necrotic tissue revealing an abundant growth of a fungus made up of branching septate mycelia with formation of spores. The lining membrane of the sphenoid showed epithelium and supporting tissue with partial squamous metaplasia and hyalin change in the basement membrane.

After operation, the patient's headache disappeared completely and at the time of her last examination on December 2, 1957, the sphenoid sinus appeared to be clean. The patient continued to be seen in the Department of Neurology because of a general feeling of depression. She was worried about a stroke and about the possibility of cancer.

<center>GROUP III</center>

<center>TWO CASES OF UNUSUAL INFLAMMATORY DISEASE OF THE
SPHENOID SINUS WHICH ARE NOT UNDERSTOOD
COMPLETELY AT THIS TIME</center>

CASE 7. B. B. UH 914077. This patient, a white female, aged 32, was admitted to the Department of Otolaryngology on November 19, 1958, complaining of chronic bilateral frontal headache, weakness, and general lassitude. She stated that she had had headaches and nasal discharge for several years which had been attributed to sinusitis. In late June of 1958 she began to have severe bifrontal headaches without other symptoms. These headaches would waken her at night. Recently the headaches were generalized with severe pain in the temporal
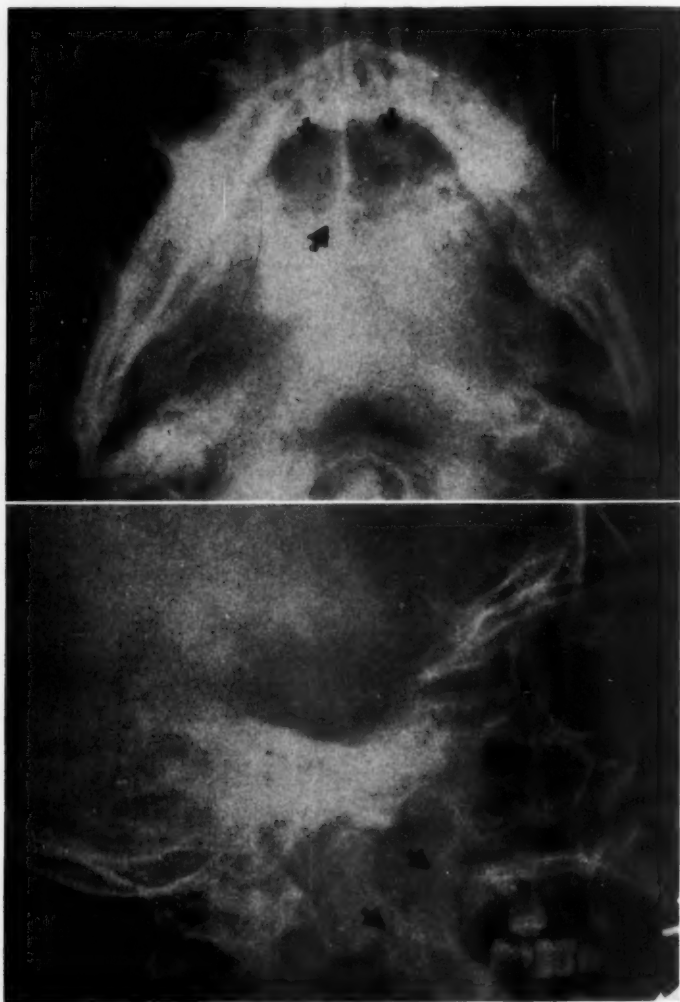
Fig. 10.—Case 9. F.T. UH 854295 Carcinoma of the nasopharynx
with extension to the base of the skull. Lateral view shows nasopharyngeal
soft tissue mass (arrows) and destruction of the clivus, posterior wall of
the sphenoid sinuses and dorsum sellae. The floor of the sella is also involved
(indistinct and demineralized). Base view shows diffuse loss of bony detail
in the midline. Smudged appearance is typical of carcinoma. Note involve-
ment of posterior walls of sphenoid sinuses (single arrow) and soft tissue
masses within sphenoid sinuses (double arrows).

and occipital regions. She stated that she had been on some form of antibiotic most of the time since June and that in September of 1958 she was hospitalized for two weeks during which time there was surgical drainage of both antra although she was told that no pus was obtained. In addition to the antibiotics, she was given corticosteroids in the form of Medrol by mouth while in the hospital and the administration of these preparations had been continued until the time of her examination at University Hospital. In delving further into her history, it was found that she never had headaches prior to eight years before, when she experienced her first frontal headache while vacationing. Recurring headaches were not incapacitating but there was one rather severe exacerbation five years before which was diagnosed as a sinus infection. The next severe exacerbation was the one mentioned in June of 1958 when she had yellow discharge from her nose which had persisted.

Examination revealed a chronically ill, thin woman, of approximately the stated age. She appeared to be unkempt, lethargic, and indifferent. She kept her hand over the left side of her forehead because of pain in the frontal area. Her temperature was 99 degrees F. and her white count 11,650. The right ear was normal but there was clear fluid seen through a transparent left tympanic membrane. There was profuse purulent exudate throughout both middle meatuses of the nose. In the nasopharynx there was a large amount of pus and what appeared to be a small mass of granulation tissue in the region of the rostrum of the sphenoid.

Roentgenograms of the skull and paranasal sinuses showed bilateral pansinusitis. There was sclerosing osteitis involving the frontal sinuses, the maxillary antra, and the sphenoid sinuses with gross thickening of the walls of the sphenoid (Fig. 7). Outside films of the chest taken on September 23, 1958, showed no abnormality.

The appearance of the patient and her general symptoms prompted thorough investigation to rule out possible brain abscess. Neurological and neurosurgical examinations showed no evidence of intracranial disease. The spinal fluid was normal. From the otolaryngological standpoint, it was felt that the findings were compatible with an osteomyelitis of the basisphenoid.

On November 26, 1958, a left external, frontal, ethmoid and sphenoid exenteration was done. The walls of the frontal sinus were

Fig. 11.—Case 10. W.B. UH 825892 Carcinoma of the sphenoid sinus with extension. Gross destruction involving sphenoid sinus, sellar floor, and clivus. Note soft tissue extension into nasopharynx, deep to normal mucous membrane (arrow).

greatly thickened and eburnated but there was no pus in the cavity and its posterior wall was intact. There was some thickening of the lining of the anterior ethmoid cells. There was a large amount of pus and granulation tissue with destruction of intercellular septa in the group of posterior ethmoid cells. Under the previously noted granulation tissue in the region of the rostrum of the sphenoid, it was found that there was destruction of bone and an obvious osteomyelitis of the sphenoid rostrum and the posterior end of the perpendicular plate of the ethmoid. The natural ostium of the sphenoid could not be found. It was impossible to perforate the anterior face of the sphenoid sinus by pressure with a curet. With difficulty, the anterior wall of the sphenoid sinus was removed with a chisel. This wall was found to be 3 to 4 mm in thickness and extremely sclerotic. Finally the posterior end of the nasal septum and the anterior walls of both sphenoid sinuses were removed revealing one large cavity filled with

thick granular material that looked suspiciously like neoplasm. Frozen section showed chronic, hypertrophic sinusitis with heavy infiltration of plasma cells. This inspissated material and the thickened mucosal lining were removed completely from both sphenoid sinuses.

The patient improved remarkably during the first four or five postoperative days. She was more alert and paid attention to her personal appearance. The headaches disappeared two days after operation.

The Department of Pathology reported that the excised tissue showed marked acute and chronic inflammatory reaction. Necrosis and the presence of giant cells were reported in some areas. The involvement of bone was in the form of an active chronic osteomyelitis. Neoplasm was considered, but a definite diagnosis could not be made. On special stains and culture, neither acid-fast bacilli nor fungus forms could be found. The pathologist stated that he could not make a definite diagnosis but felt that midline lethal granuloma must be strongly suspected.

Another chest x-ray was taken which demonstrated a 2 to 2½ cm rounded density in the right para-hilar region. The roentgenographic appearance suggested a granuloma.

It will be recalled that this patient had been given steroid therapy in the form of oral Medrol since September. In preparation for the operation, she was therefore given I.M. cortisone acetate on advice of the Department of Endocrinology and Metabolism. It was thought that her immediate postoperative improvement might be on the basis of steroid therapy, if the diagnosis of lethal midline granuloma was correct.

The diagnosis of lethal midline granuloma was difficult to accept in the presence of obviously long standing sclerotic sphenoiditis with marked thickening and eburnation of the sinus walls, and the presence of inspissated pus and rather avascular granulation tissue within the sinus. However, the granulomatous lesion in the lung continued to increase in size and showed radiographic evidence of excavation (Fig. 8). There continued to be profuse purulent rhinorrhea. At this writing, January 1, the patient is comfortable and has gained
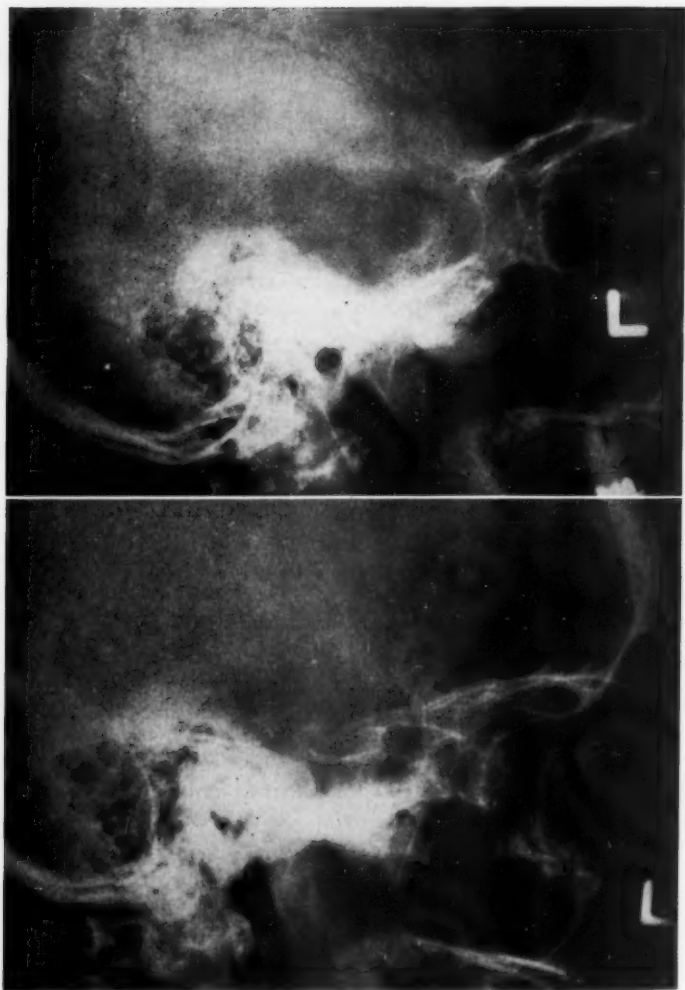
Fig. 12.—Case 11. A.D. UH 716282 Pseudoadenomatous basal cell carcinoma (malignant cylindroma) of sphenoid sinus. (a) Lateral view shows the large area of bone destruction about the sella. (b) Lateral projection shows remarkable bone regeneration one year after radiation therapy.

some weight. There is thick, purulent discharge on each side of the nose and slightly exuberant granulation tissue around the large opening in the sphenoid sinus. She is being continued on steroid therapy.

CASE 8. C. J. UH 893900. This patient, a white male, aged 65, was registered in the Department of Otolaryngology on February 26, 1958. At that time he complained of pain in the left supraorbital region and total blindness in his left eye. He had had chronic heart disease but there were no complaints associated with his present illness until August of 1957 when he noticed excessive lacrimation from the left eye. He then began to have some pain in the nasal corner of the left eye and noted nasal discharge which was blood tinged. At that time he had his "lacrimal duct opened" without relief of symptoms. In January, 1958, he began to lose vision in his left eye and indicated that it was his central vision that disappeared first. This progressed to total blindness during which time he noticed that his left eye became prominent. The prominence of the left eye had been increasing during the month prior to his examination.

Examination of the nose revealed a little purulent exudate in the left middle meatus. There was a little neoplastic appearing edematous granular tissue in the region of the left spheno-ethmoidal recess which could be seen on anterior rhinoscopy and with a nasopharyngeal mirror. The left eye showed slight proptosis, complete ophthalmoplegia, and total loss of vision.

Roentgenograms of the skull and paranasal sinuses demonstrated an overall density of the sphenoid sinus and an apparent defect in the anterior wall of the sella turcica. Laminagrams (sections did not go all the way through the sella turcica) failed to demonstrate the defect in the anterior wall of the sella but did show a large defect in the anterior wall of the sphenoid sinus. The very dense sclerosis of the anterior inferior aspect of the sphenoid sinus suggested long standing inflammatory disease rather than neoplasm (Fig. 9).

A biopsy specimen was removed from the region of the left spheno-ethmoidal recess which showed polypoid hyperplasia of sinus mucous membrane with heavy infiltration of plasma cells and fibroblasts in the submucosa. Some liquefaction necrosis was present. The plasmocytic infiltrations were heavy and the diagnosis of a plasmocytoma was considered but the pathologist favored an inflammatory
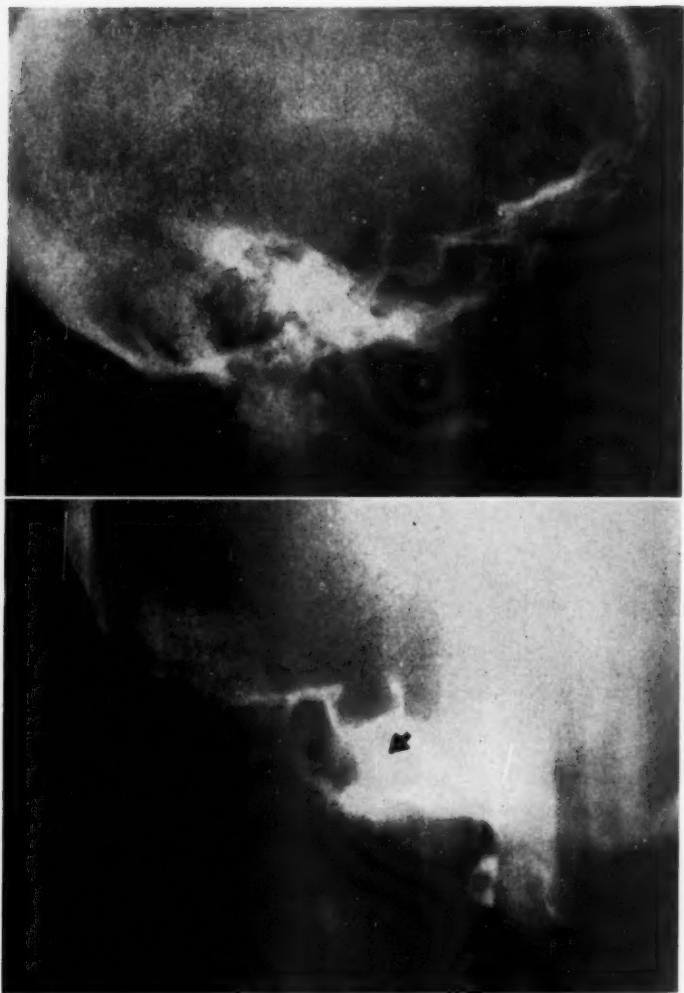
Fig. 13.—Case 12. J.K. UH 833210 Pituitary carcinoma presenting in the sphenoid sinus. (a) Sella considered within normal limits although fairly long in comparison to vertical diameter and slightly irregular floor. Note soft tissue mass in sphenoid sinus (arrow). (b) Laminagrams fail to demonstrate any defect in sellar floor. Soft tissue mass outlined by air anteriorly (arrow). Posterior wall of smaller sphenoid sinus posteriorly (arrow).

process over neoplasm. He suspected that the lesion might represent a variant of a lethal midline granuloma.

On March 28, 1958, a submucous resection of the septum and left sphenoidotomy were done. On removing the anterior face of the left sphenoid, the surgeon noticed that there was a large cavity filled with tissue which appeared to be neoplastic. The pathological diagnosis was that of a plasma cell granuloma.

Since the patient continued to have pain in the left supraorbital region which was getting more and more severe, a frontal-ethmoid-sphenoid exenteration was done on April 29, 1958. It was found that the granuloma had invaded the dura in the posterior ethmoid region and it was impossible to remove all of it. Postoperatively, the patient developed a hemorrhage which extended beneath the dura and he expired.

Necropsy showed subarachnoid and intraventricular hemorrhage. There was a plasmocytic granuloma involving the ethmoid and sphenoid sinuses with erosion of the left orbit, roof of the sphenoid sinus, the cribriform plate, and producing destruction of the left optic nerve. The final diagnosis was a plasmocytice granuloma and the question was raised regarding the possibility of this being a variant of a lethal midline granuloma.

GROUP IV

A GROUP OF CASES OF NEOPLASTIC DISEASES INVOLVING THE SPHENOID WHICH ARE PRESENTED IN AN EFFORT TO EMPHASIZE THE IMPORTANCE OF HIGHLY CRITICAL EVALUATION OF RADIOGRAPHS

CASE 9. F. T. UH 854295. This patient, a white male, aged 62, was admitted to the Neurology Service on October 4, 1956. He complained of severe headaches in the frontal region and in the back of the eyes of three months' duration. Gradually there had developed ptosis of the left upper eyelid and proptosis of the left globe. A period of hospitalization elsewhere had not resulted in a definite diagnosis. Shortly before his admission to University Hospital, the right eye also became prominent.

Fig. 14.—Case 13. A.S. UH 708514 Chromophobe carcinoma of the
pituitary. Bone erosion about sella so extensive that intrasellar origin not
apparent. Preservation of dorsum compared to erosion of tuberculum sellae
is against suprasellar origin. Clivus obscured by mastoid air cells.

Examination revealed bilateral proptosis and bilateral ophthal-
moplegia. Vision in the right eye was 20-40 plus 3 and in the left
eye 20-50 plus 1.

On otolaryngological examination a large vascular tumor was
found to be filling the vault of the nasopharynx. A biopsy specimen
showed medullary masses of poorly differentiated noncornifying
squamous cell carcinoma.

Conventional skull films with supplementary base views showed
a soft tissue mass in the nasopharynx and extensive bone destruction
involving the sella turcica, posterior sphenoid sinuses, and clivus
(Fig. 10).

Radiographic interpretation suggested carcinoma of the nasopharynx with extension to the base of the skull. A carcinoma in this region is a lesion most apt to produce changes of this nature.

CASE 10. W. B. UH 825892. This patient, a white male, aged 63, was admitted to the Department of Otolaryngology on December 5, 1955. He complained of sharp shooting bifrontal headaches of seven months' duration and mucoid nasal discharge that had been present for about five months. Six weeks prior to admission, his headaches ceased and he suddenly developed double vision with some blurring.

Examination showed a paralysis of the right lateral rectus muscle. The visual fields were normal. Nasopharyngeal examination showed a very definite prominence in the vault of the nasopharynx which was covered with normal appearing mucous membrane. The submucosal mass seemed to be the most prominent just inferior to the rostrum of the sphenoid. There was no evidence of any surface neoplasm.

Conventional skull films showed a large soft tissue mass in the nasopharynx and extensive bone destruction involving the floor of the sella, posterior sphenoid sinuses, and clivus (Fig. 11). Base views were not obtained. Bilateral carotid angiograms were normal.

An incision was made in the nasopharyngeal mucous membrane and a biopsy specimen was removed from the submucosal neoplasm immediately below the rostrum of the sphenoid. The pathological diagnosis was cornifying squamous cell carcinoma.

During the performance of a right external ethmoid-sphenoid exenteration, it was found that neoplasm filled the sphenoid sinus and had replaced the bone of the basisphenoid, and clivus back of which there was neoplastic invasion of the dura.

The radiographic evidence of a soft tissue mass in the nasopharynx and extensive destruction of the sphenoid bone gave the radiologist the impression that this was probably a carcinoma of the nasopharynx with extension to involve the base of the skull. In this particular case, however, the neoplasm was apparently primary in

the sphenoid sinus and had extended submucosally beneath the mucous membrane of the nasopharynx.

CASE 11.   A. D.   UH 716282.   This patient, a white female, aged 44, was admitted to the Department of Neurology on November 6, 1951.   Her chief complaint was loss of vision and pain in the right eye and numbness in the right cheek of one year's duration.

Examination of the nose and nasopharynx revealed no abnormality.

Conventional projections of the skull showed a large area of bone destruction which involved the planum sphenoidale, the entire sella and clinoids, the clivus, and the sphenoid sinuses (Fig. 12).   The radiographic appearance indicated neoplastic destruction but this was so extensive that the point of origin was indeterminate.

A transseptal sphenoidotomy was done and a biopsy specimen of the tumor was removed.   The pathological diagnosis was pseudo-adenomatous basal cell carcinoma (malignant cylindroma).

This patient was afforded temporary palliation through radiation therapy.   It is interesting to note the remineralization of the sella one year after therapy was instituted.

CASE 12.   J. K.   UH 833210.   This patient, a white female, aged 23, was admitted to the Department of Urology on January 25, 1956, complaining of menstrual irregularities, backache, and hirsutism.

Conventional skull films showed the sella turcica to be within normal limits.   There was a soft tissue mass noted in the sphenoid sinus.   Since a clinical history of acromegaly was provided, and a tentative diagnosis of eosinophilic adenoma of the pituitary gland suspected, the radiologist felt that the soft tissue mass in the sphenoid sinus represented a pituitary adenoma.   Laminagraphy failed to demonstrate any bony defect in the floor of the sella (Fig. 13).

Examination in the Department of Otolaryngology revealed no significant abnormality.   The nose and nasopharynx appeared to be normal.   On the basis of the clinical and radiographic findings, a
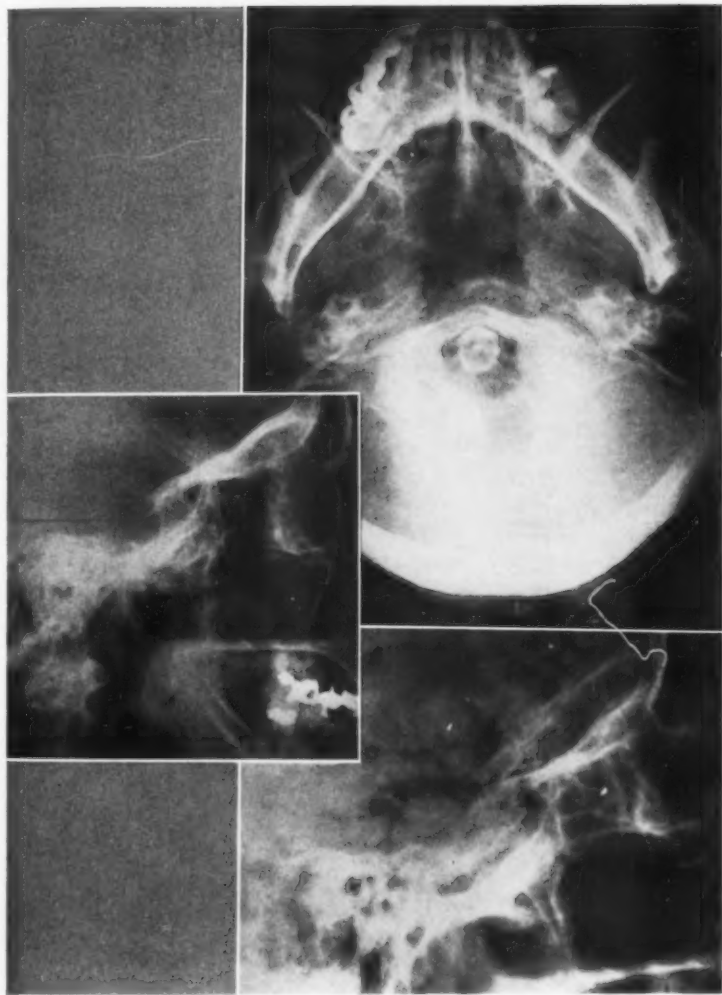
Fig. 15.—Case 14. M.S. UH 815839 Chordoma of the clivus. Base view shows midline destruction with precise margins. Lateral view shows destruction of the clivus, posterior aspect of sphenoids, and dorsum sellae, but sparing the anterior floor of the sella. Lateral view of pneumoencephalogram shows soft tissue mass (arrows).
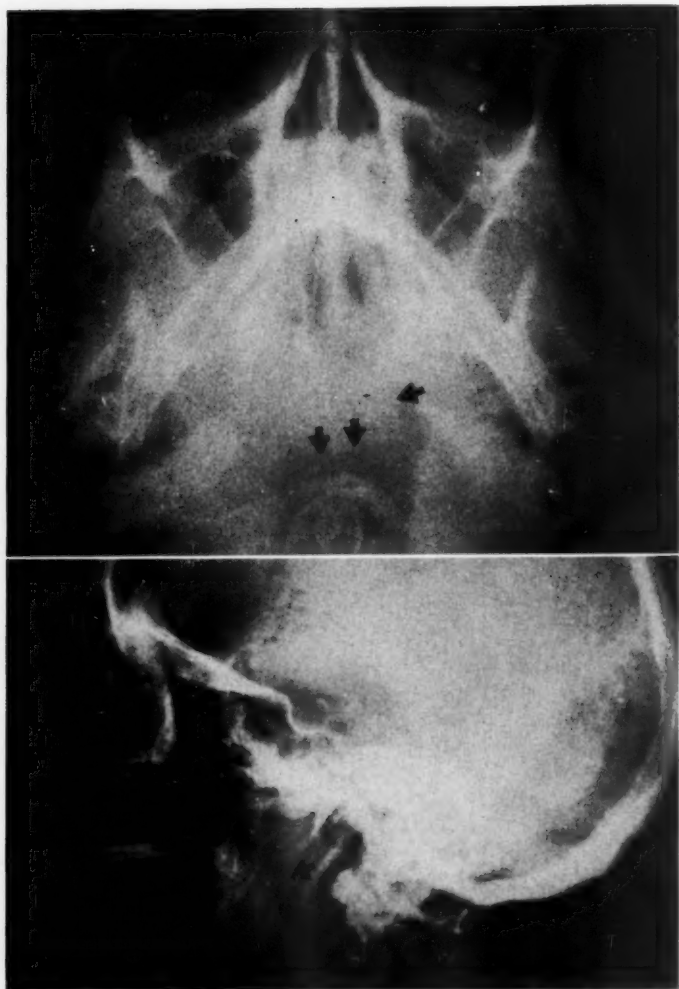
Fig. 16.—Case 15. C.K. UH 882565 Chordoma of the clivus. Lateral view shows soft tissue mass displacing the posterior wall of the nasopharynx (arrow). Base view shows extensive soft tissue mass extending across the midline encroaching on nasopharyngeal air shadow (vertical arrows). The right side of the clivus is eroded; note intact left side (horizontal arrow).

submucous resection of the nasal septum and transseptal sphenoidot-
omy with biopsy of neoplasm in the sphenoid was performed under
local anesthesia on February 3, 1956. The patient experienced no
pain during the submucous resection of the septum or removal of the
anterior wall of the sphenoid. After opening the sphenoid sinus, a
small purplish tumor mass was visualized in the posterior aspect of the
roof of the sinus. On touching this tumor with a probe, the patient
screamed with pain which she said was in both frontal and both
temporal areas. The local application of 10 per cent cocaine on a
cotton tampon failed to prevent this pain on manipulation. A small
specimen of tissue was removed and the pathological diagnosis of
chromophobe adenoma, possibly an adenocarcinoma of the anterior
pituitary was obtained.

The patient was given radiation therapy during the spring of
1956.

Bouts of severe frontal headaches recurred in December of 1956
and after a period of temporary relief, they returned in February
and March of 1957. After six months' freedom from symptoms, she
developed severe continuous frontal, retro-orbital and occipital head-
aches in October of 1957. Radiographs showed an increase in size of
the mass within the sphenoid sinus but no apparent change in the
sella turcica.

On November 27, 1957, a left external ethmoid and sphenoid
exenteration was done under general anesthesia. The ethmoid laby-
rinth appeared to be normal. On exposing the anterior face of the
sphenoid it was noted that a little purplish tissue presented at the
sphenoid ostium. On removing the anterior wall of the sphenoid
sinus, it was found that the cavity was filled with a purplish, appar-
ently neoplastic, mass of tissue. No point of attachment of the tumor
could be determined; and after cleaning out the sinus completely
there was no evidence of dehiscence in the posterior or superior wall
of the sinus either on inspection or palpation with a probe. Also,
there was no evidence of infiltration of bone.

The pathology report indicated a well differentiated pituitary
adenocarcinoma.

In the Department of Radiation Therapy it was felt that further
radiation was contraindicated. The patient had an uneventful con-

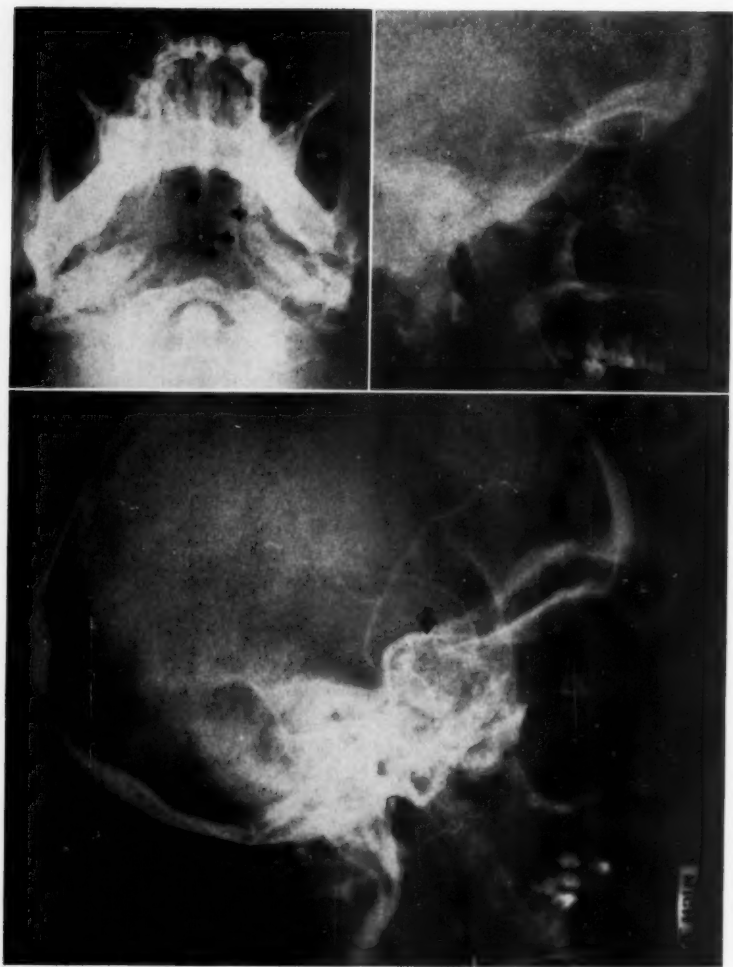Fig. 17.—Case 16. F.T. UH 757439 Solitary plasmocytic myeloma. Base view shows unilateral erosion of clivus (horizontal arrows) involving posterior walls of sphenoid sinus (vertical arrow). Lateral view shows erosion of the sellar floor and sphenoid sinuses. Lateral carotid angiogram shows large vascular tumor stain apparently extending outside skull through the middle fossa. Carotid displaced and occluded (arrow).

valescence and after the operation was free from headaches. At the time of her last examination in September, 1958, there was no evidence of recurrent tumor in the open sphenoid sinus and palpation of the interior of the sinus with a probe caused no pain.

CASE 13. A. S. UH 708514. This patient, a white male, aged 34, was admitted to the Endocrinology and Metabolism Division of the Medical Service on July 9, 1951. He was semicomatose, irrational, sweating, and belligerent. It was determined that he was in diabetic acidosis and after this was controlled he was discharged from the hospital. His next admission was in May of 1952 at which time he was complaining of attacks of vertigo, and numbness and tingling of the left side of his body which lasted about 20 minutes and occurred about twice a week. During the preceding two months he had complained of sharp bifrontal headaches.

Examination of the nasopharynx showed a smooth prominence covered with blood-tinged mucus in the left spheno-ethmoidal recess area.

Conventional views of the skull showed gross destruction in the region of the sella including the tuberculum sellae and the anterior clinoids. The sellar floor was eroded and the sphenoid sinus was involved. The dorsum sellae was only partially decalcified. The clivus was obscured by mastoid air cells (Fig. 14). No base view was obtained. Due to the very extensive bone destruction in the region of the sella, the etiology and site of origin could not be determined by the radiologist.

The patient's headache became increasingly severe and involved the temporal region and the vertex. A biopsy specimen was taken from tissue in the left spheno-ethmoidal recess region on May 12, 1952, and revealed a medullary, malignant neoplasm of the carcinomatous type. The pathologist favored the diagnosis of a chromophobe carcinoma of the anterior pituitary. Radiation therapy was administered. Death occurred November 20, 1952, in another hospital where autopsy was not performed.

CASE 14. M. S. UH 815839. This patient, a white female, aged 56, was admitted on the Neurology Service on July 7, 1955, complaining of severe frontal and parietal headaches of one month's

duration. A definite diagnosis was not made at this visit. She was re-admitted to the hospital on January 9, 1956, again complaining of right parietal headaches and numbness of the left side of her face. It was noted that there was a paralysis of the right medial rectus and superior oblique muscles.

Conventional skull films with supplementary base views showed extensive midline bone destruction involving the entire clivus, the dorsum sellae, the posterior aspect of the sphenoid sinuses, and the posterior half of the floor of the sella. A pneumo-encephalogram showed a soft tissue mass in the area of bone destruction. Laminagraphy excluded calcification in this mass (Fig. 15).

Although examination of the nose and nasopharynx showed no abnormalities, the radiographic findings prompted a transnasopharyngeal biopsy. An incision was made in the vault of the nasopharynx inferior to the sphenoidal rostrum. A large submucosal neoplastic mass was encountered which was obviously replacing bone. The pathology report indicated a chordoma.

Postoperatively the patient developed a subarachnoid hemorrhage and expired. At necropsy a very extensive chordoma with intracranial extension was found.

CASE 15. C. K. UH 882565. This patient, a white female, aged 58, was admitted to the Department of Otolaryngology on September 25, 1957, with a chief complaint of difficulty in swallowing. The history indicated that in 1951 she had developed a paralysis of the tongue. In 1953, she began to have difficulty in swallowing and speaking. In 1954 it was noted that the left eye turned in. Tube feedings had to be instituted in 1956. In August of 1957 a biopsy specimen was taken from a lesion that was discovered in her nasopharynx and a pathological diagnosis of chordoma was made. Six weeks prior to admission to University Hospital a tracheotomy had been required because of dyspnea which had been increasing over a period of eight months.

On examination, it was noted that there was a paralysis of the left lateral rectus muscle, the left side of the tongue, the right side of the palate, the pharyngeal constrictor muscles, and both vocal cords. In addition to these complete paralyses, there was fibrillary

twitching on the right side of the tongue and marked weakness of the left side of the palate. Mirror examination of the nasopharynx revealed a large definitely submucosal tumor in the vault.

Routine skull projections with base views showed a large soft tissue mass in the nasopharynx posteriorly. There was erosion of the clivus on the right side. The long history and multiple cranial nerve involvement led the radiologist to suspect the presence of a chordoma despite bone involvement off the midline (Fig. 16).

After consultation with the Departments of Neurology, Neurosurgery, and Radiation Therapy, it was decided that an operation should be performed in an effort to effect decompression of the medulla.

On October 30, 1957, a left external ethmoidectomy approach was used for the partial removal of the chordoma. After the ethmoidal labyrinth had been exenterated, the sphenoid sinus was opened and found to be uninvolved by neoplasm. The nasopharyngeal mucous membrane over the floor of the sphenoid was elevated and the floor of the sphenoid sinus removed revealing a tumor which had replaced the basisphenoid. A large amount of tumor was removed but no effort was made to remove all of it for it was essential that further injury to the brain stem be avoided. The patient was discharged from the hospital on November 11 at which time there was no change in her cranial nerve palsies.

CASE 16. F. T. UH 757439. This patient, a white female, aged 39, was admitted on the Neurology Service on March 31, 1958, complaining of numbness and tingling and later severe pain over the right side of her face. Her symptoms began six months prior to this examination, and two months before, she developed diplopia and noted that the right eye turned in and the right upper lid drooped.

Neurological examination revealed a right partial third nerve paralysis, a right sixth nerve paralysis, and weakness of both the sensory and motor divisions of the fifth nerve.

Otolaryngological examination showed no evidence of abnormality in the nose or nasopharynx.

Conventional skull films with supplementary base views showed a large sharply marginated bone defect involving the right side of the clivus, the posterior sphenoids, and the floor of the sella. A right carotid angiogram demonstrated a large extremely vascular tumor in the mesial aspect of the right middle cranial fossa. The carotid siphon was straightened and the internal carotid occluded at the level of the tuberculum sellae (Fig. 17). The radiographic findings indicated a large, very vascular tumor of the right parasellar area with underlying bone destruction.

On April 18, 1958, a frontoparietal osteoplastic craniotomy was performed in the Department of Neurosurgery. A mid-fossa tumor was exposed which seemed to have an extradural origin in the region of the base of the skull. This tumor was exceedingly vascular and only partially removed.

The pathological diagnosis was plasmacytoma and it was felt that the lesion had arisen from bone. Postoperatively the patient was given radiation therapy.

SUMMARY AND CONCLUSIONS

In this presentation an attempt has been made to give the sphenoid sinus a bit of an airing and it is to be hoped that it will not be returned immediately to its accustomed place of neglect.

A review of the literature citing instances of sphenoidal mucoceles or pyoceles discovered at autopsy, uncapped during inordinate transdural operations for suspected brain tumors, or surgically drained as an afterthought following radiation therapy for a supposed sphenoid or pituitary malignancy provides a sad commentary on the general recognition of isolated sphenoid disease.

This study has provided six items of particular interest:

1. The fact that only one patient in the first two groups of this series was referred directly to the Department of Otolaryngology supports the previously expressed contention that the sphenoid remains out of sight and out of mind. One patient with an orbital apex syndrome was admitted to the ophthalmology Service, while the

other four, including the two patients with mucocele, were referred to the Department of Neurology as a last resort.

2. There is good evidence that low grade chronic, inflammatory diseases of the sphenoid may exist for years before producing symptoms of sufficient severity to prompt the patient to seek medical help. In Case 2, there was severe bifrontal headache of sudden onset and eight weeks' duration; in Case 5, there was sudden onset of the headache which had been present for eight months; in Case 6, there was a two months' history of severe headache which had sudden onset although the patient had had intermittent headaches for many years which had been diagnosed as migraine. In each of these cases, there was either marked sclerosis and proliferation, or extensive destruction of bone which obviously had been years in development.

3. In cases of chronic sphenoid suppuration which have an opportunity for drainage, in contrast to the closed lesions such as mucoceles or pyoceles, a thorough history may reveal evidence of long remissions and acute recrudescences of headache not necessarily associated with upper respiratory infections.

4. In Cases 2 and 6, there was very extensive sclerosis of the walls of the sphenoid sinuses. In each of these, culture of the contained pus revealed an abundant growth of fungi. These were accepted as secondary invaders, but unfortunately were not identified positively. One wonders if their presence might have been related to the proliferation of bone.

5. It has been demonstrated that obscure cases of isolated sphenoid suppuration and cases of sphenoidal mucocele or pyocele will submit to pre-operative diagnosis prior to the onset of an orbital apex syndrome providing the history and examination are adequate, providing the rhinologist maintains a high index of suspicion regarding the sphenoid, and providing radiographic studies are complete and subjected to highly critical evaluation.

6. In a soul searching mood, I frankly wonder how many cases of obscure chronic sphenoiditis I have missed in patients who have come to my office with the chief complaint of "Doc, I've got a sinus."

University of Michigan Medical Center

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XXXII

CONCERNING THE CRITERIA OF OPERABILITY IN LARYNGEAL CANCER

JOHN J. O'KEEFE, M.D.

PHILADELPHIA, PA.

Early in the care of the patient with laryngeal cancer, we are confronted with the decision to operate, and must select a method or technique appropriate to the task. Such a selection has to be based on an all-inclusive appraisal of the patient and his tumor, and have as its primary intention, the best chance of cure. In many instances this is a complex procedure, beset with problems of classification, influenced by the limitations of one's personal surgical experience, and to a lesser extent, by the experiences of others.

Many of the factors that contribute to the complexity of this problem are a direct consequence, although an inadvertent one, of the growth and development of laryngeal surgery over the past two or three decades. By having extended its scope so as to incorporate cancer of the paralaryngeal structures as integral parts of its field, and by having claimed the prerogative of operating upon the neck for the malignant metastases of laryngeal cancer, laryngeal surgery has been enriched, or encumbered, with the techniques devised to accommodate the lesions of these anatomic parts. Currently, with the apparent increased concern for the preservation of structure and function in laryngeal cancer surgery—an attitude that necessarily does not disregard the malignant nature of this disease, but more likely is a reflection of investigative thought questioning the validity of the criteria of operability—still further techniques, but of a conservative rather than of a radical nature, have been proposed and added to our armamentarium. Numerically, if for no other reason, all of these additional procedures, radical and conservative, tend to make the selection of the operation of choice a more difficult one to determine.

Contributing to this same vein of thought, it is also appreciated that to formulate a complete classification of a malignant laryngeal lesion is not always a simple matter. Although readily accessible to mirror and direct view, examination of the larynx may be deficient, often failing to provide full visualization of the tumor mass, and neither permitting an accurate determination of its site of origin, nor a real estimate of its degree of invasion. Commonly too, efforts to determine the presence of cervical metastases by palpation of the neck are frequently futile, if not misleading. Yet an appreciation of these characteristics is critical to proper classification. Consideration of other characteristics is necessary to the complete determination of degree of malignancy, but of basic importance is a knowledge, first, of the location or origin of the tumor, and secondly, of the presence or absence of cervical metastases. The former infers the ability of a laryngeal tumor to metastasize; the latter, its ultimate prognosis.

Apropos of this brief survey of the basic tenets of laryngeal cancer, and of laryngeal cancer surgery, the following study will consider, or reconsider, the various criteria employed in the selection of operation for cancer of the larynx, and as far as is feasible, will attempt to ascertain which are consistent with good judgment and safety.

EVALUATION OF OPERATIVE PROCEDURES

Failures in the surgical management of cancer of the larynx are due to an inadequacy of the primary operation. When the magnitude of the primary operation is less than total laryngectomy, i.e., following any form of cordal resection, such as the laryngofissure operation, the endolaryngeal resection technique, or partial laryngectomy, evidence of failure is usually observed as local recurrence. Only occasionally are such failures first manifested by cervical metastases. Laryngectomy failures, conversely, occur commonly as cervical metastases, and unusually as local recurrences. Needless to say, in many instances initial evidence of failure in the treatment of this malignancy is recognized through the identification of a remote or organ metastasis, regardless of the type of primary operation.

The data referred to in this report have been gathered from the Laryngological Service at Jefferson Hospital, Philadelphia, which, during part of the period of time encompassed by this report, was

directed by Dr. L. H. Clerf. I wish to acknowledge my indebtedness
to him for permission to report on this material.

CORDAL CANCER

A carcinoma entirely contained on the membranous portion of
one vocal cord is ideally suitable for removal by any method of cordal
resection. The laryngofissure technique is the most commonly utilized
of these methods and is the operation of choice in such instances.
There is no controversy concerning the management of lesions con-
forming to this definition; resection of the involved vocal cord is
tantamount to cure.

Additionally, however, in a certain number of instances, one sees
malignant cordal growths that fail to conform to the limitations
of this definition, but in which it is assumed that resection can be
accomplished through this same approach. Most commonly included
in this group are lesions involving the anterior commissure, bilateral
cordal lesions, cordal lesions extending posteriorly without limitation
of motility, and cordal lesions showing limited extension into the
ventricle or subglottically. Since the classical laryngofissure opera-
tion, characterized as it is by simplicity of technique and limitation of
application, has already been adjudged an inadequate method of
resecting these more extensive cordal lesions, the "anterior commis-
sure" techniques and several variants of partial laryngectomy have
been proposed as alternative methods. Although they apparently have
ably compensated for the technical limitations and restrictions of
cordal resection by median thyrotomy, controversy exists as to wheth-
er or not they are properly selected in lieu of laryngectomy, as pro-
cedures of choice for the resection of these more extensive forms of
cordal cancer.

In a previous report (published in 1955) relative to 371 determi-
nate and consecutive cases of cordal cancer that had been operated
upon by the technique of thyrotomy, 51 instances of local laryngeal
recurrence were disclosed to have shown, at the time of operation,
extension of tumor to the anterior commissure in 32 cases, of sub-
glottic extension in 14, and of lateral extension of the cancer into
the ventricle in 5 cases. Appropriately enough, these failures were
self-criticized as being "attributable either to having selected thyrot-
omy improperly, or to an attempt to extend the technique of thy-

TABLE I

CORDAL CARCINOMA
FAILURES FOLLOWING RESECTION

OPERATION	NUMBER OF CASES	NUMBER OF FAILURES	PERCENT FAILURES
Laryngofissure	96	5	5.2
Anterior Commissure Technique	41	9	21.4
Partial Laryngectomy	17	14	82.3

rotomy to accommodate lesions that had grown beyond the confines of the vocal cord."

By contrast, in this study, which concerns only the patients treated surgically between 1950 and 1955, an additional 154 cases of cordal cancer were selected for operation accordingly as they met with criteria which adjudged them as suitable either for laryngofissure, for the anterior commissure technique, or for partial laryngectomy.

Ninety-six of the 154 cases were classified as intrinsic and ideally suitable for laryngofissure. Interestingly enough, in spite of meticulous efforts at classification, operative failure in this group occurred in 5 instances; as local recurrence in 4 cases, and as cervical metastasis in one. Forty-one cases, classified as cordal but with extension to the anterior commissure, were operated upon by one of the several "anterior commissure" techniques. There were 9 failures; 5 as local recurrences, and 4 as metastases to the regional lymph nodes. The remaining 17 patients, classified as cordal but with extension either posteriorly (without fixation) or subglottically, were operated upon by a partial laryngectomy technique. Failures attributable to this surgical method occurred in 14 cases; as endolaryngeal recurrences in 6, and in 8 as cervical lymph node metastases (Table I).

An additional group of patients with cordal cancers, either originating posteriorly or extending posteriorly, and with fixation of the arytenoid, were classified as already too far advanced to be considered for any operative method less than total, wide-field laryngectomy.

TABLE II

ADVANCED CORDAL CARCINOMA
CERVICAL NODES NEGATIVE

FAILURES FOLLOWING LARYNGECTOMY		FAILURES FOLLOWING LARYNGECTOMY WITH NECK DISSECTION	
Patients Operated Upon	79	Patients Operated Upon	29
Failures	19	Failures	4
Per Cent Failure	24.0	Per Cent Failure	13.8

Their obvious degree of infiltration refutes the probability of successful resection by any restricted procedure.

EXTRACORDAL CANCER

Cancers of the larynx that originate either above or below the true vocal cords are more malignant than cordal ones. Their early growth is usually asymptomatic, and when first seen may already have attained a formidable size; anatomically they are predisposed to metastasize early and with relative ease; and in some instances extension of the primary growth may be such as to preclude surgery as a feasible method. These characteristics, emphasizing the highly malignant potential of these lesions, are sufficient reason to eliminate all thoughts of conservatism in their surgery. When free of palpable cervical lymph nodes, total laryngectomy is accepted as the basic technique applicable for the resection of such lesions. There is sufficient reason, however, considering the high incidence of metastases associated with them, to question the adequacy of this method. In contrast to the preceding discussion, the controversy here then, is whether or not a technique more extensive than laryngectomy is indicated as the primary surgical method.

The second portion of this study is presented in consideration of this controversy, and consists of three groups of patients, each representative of one of the several parts comprising their classification. First, total laryngectomy was selected as the primary operative procedure in instances of advanced cordal cancers, which were adjudged pre-operatively to have impalpable cervical lymph nodes. There were

TABLE III

EXTRACORDAL CARCINOMA
FAILURES FOLLOWING LARYNGECTOMY WITH NECK DISSECTION

CERVICAL NODES POSITIVE		CERVICAL NODES NEGATIVE	
Patients Operated Upon	56	Patients Operated Upon	40
Failures	21	Failures	5
Per Cent Failure	37.5	Per Cent Failure	12.5

79 patients so classified, and so operated upon. Failures, as cervical metastases, occurred in 19 instances—approximately 25 per cent. An additional 29 patients, similarly classified, were subjected to a one-stage laryngectomy and neck dissection technique as the primary operation: 25 are living and well and free of metastasis; there were 4 failures—13.8 per cent (Table II).

Secondly, 56 patients with extracordal cancers, originating either subglottically or supraglottically, and with palpable cervical lymph nodes, were operated up by combined laryngectomy and neck dissection. There were 21 failures—37.5 per cent.

The third group of patients, classified as having extracordal cancers but with impalpable cervical lymph nodes, were also operated upon by means of one-stage laryngectomy and neck dissection. Forty patients conformed to this classification: operative failures occurred in 5 instances—12.5 per cent (Table III).

COMMENT

This consideration of the surgical treatment of laryngeal cancer derives from an implicit appreciation of its malignant nature, holding as self-evident that whenever untreated or mistreated, it will cause the death of its host. Such a disease cannot be bargained with: more radical procedures cannot be held in reserve in event of failure of a conservative or less radical primary procedure.

Appraising the criteria of operability, as a means of selecting the operation of choice, essentially consists in evaluating or interpreting the characteristics pertaining to a tumor: substantially this amounts to classification. A classification of cancer of the larynx, based solely on anatomic principles, must necessarily be an inadequate one—for obviously growth and invasion of cancer is not delineated by anatomic planes—and therefore it follows that an operative technique devised on like principles is also inadequate.

When entirely contained on the membranous cord, a high percentage of cordal cancers are successfully operated upon by any form of cordal resection. If then, we grant an operator's ability to perform a valid procedure technically, it must be that such success is accountable only to the fact that these lesions are so contained. The operative methods previously referred to, that have been especially devised as alternative procedures of choice for the resection of extensive cordal cancers, are undoubtedly technical masterpieces. Undoubtedly too, they have been rewarded with some measure of success. Unfortunately, more than a modest amount of objective evidence strongly suggests their inadequacy: it further suggests that the criteria by which such methods are selected, are of questionable validity.

The adequacy of the surgical resection of extracordal cancers by laryngectomy alone, poses another problem: in view of the malignant potential ascribed to them, as reflected in their high incidence of post-operative cervical metastases, would not the best chance of cure for such lesions be more certainly secured by a more radical or more extensive primary operative procedure? Statistically this is so: the prophylactic one-stage laryngectomy with neck dissection is a far more rewarding method for the resection of subglottic and supra-glottic cancer than is laryngectomy alone. Admittedly, in abiding by this principle, a certain amount of unnecessary surgery would be done, but according to present-day standards, little or no additional morbidity or mortality would result from such surgery.

CONCLUSION

The intent of this presentation has been to help clarify the issue of conservative vs. radical in the surgical treatment of laryngeal cancer. In reconsidering the various criteria by which the operation

of choice is currently selected, evidence is presented that reflects adversely on their validity: some operative methods based on these criteria have been found inadequate.

It is reiterated that in the treatment of this cancer, as with cancer of other parts of the body, the selection of the operation of choice should have as its primary intention, the best chance of cure.

255 SOUTH 117TH ST.

ANATOMICAL OBSERVATIONS CONCERNING
THE LARYNGEAL APPENDIX

Edwin N. Broyles, M.D.

Baltimore, Md.

The laryngeal appendix or saccule is a pouch that arises from the anterior upper portion of the ventricle of Morgani. My interest in this pouch was stimulated by the fact that on examining several fresh larynges following laryngectomy, the large size of the laryngeal saccule present on several occasions was impressive. Many papers have been written on laryngoceles and laryngeal cysts and their treatments. What really brought about this effort was an attempt to explain certain cases of chronic laryngitis and also explain those rare cases of malignant new growths of the larynx where repeated biopsies failed to establish the diagnosis. I have not been able, so far, to definitely prove that these pathological conditions arise in the saccule but I do wish to bring to your attention the fact that in a relatively large number or percentage of larynges, the laryngeal saccule is a large cavity and is potentially a hidden source of infection or new growth.

Fifty fresh adult larynges removed at autopsy, or 100 ventricles, were examined as to the size of the laryngeal saccule. None of the medical histories of the patients indicated laryngeal symptoms. Forty-five per cent of the larynges were from colored persons and 55 per cent were from white persons. Roughly, twice as many large saccules were found in the specimens from white persons as were found in those from colored persons and slightly more enlarged saccules were found in males than in females, in the ratio of 3 to 2. Although the ages of the patients were from 19 to 96 years, most specimens were from patients in the fifties, sixties and seventies.

A larynx preserved in formalin proved too indurated for a satisfactory examination of the laryngeal saccule. Chevalier Jackson[1] writes of an enlarged saccule as an internal laryngocele. Sir Victor Negus[2] in his work, "The Mechanism of the Larynx," comes to the conclusion that in man the laryngeal saccule has no vocal functions. Professor Karl von Bardeleben[3] in his "Handbuchs der Anatomie des Menschen" feels that the laryngeal saccule pours mucus down over the vocal cords and lubricates them. The saccule is mentioned by Professor George A. Piersol[4] in his "Human Anatomy" and by Jackson and Jackson in their "Disease of the Nose, Throat and Ear." An illustrated paper by Mr. John Hilton[5] gives an excellent description of the laryngeal saccule.

In 75 of the 100 laryngeal saccules, all of which were lined with ciliated epithelium, the saccules extended up 6 to 8 mm. In 25 per cent of the saccules, the depth of the cavity extended 10 mm or more and in 7 per cent the cavity extended 15 mm or more. There was then in many larynges a fairly large cavity that may house infection or a new growth.

An attempt was made to diagnose the presence of an enlarged saccule in the living by means of x-ray and we were surprised by the clear showing in tomographs of the enlarged saccules. In the study of the saccules it was found that there were enlarged bilateral saccules in ten and enlarged unilateral saccules in five larynges.

This is a ratio of two to one or twice as many bilateral enlarged saccules as unilateral. If then, a patient has one enlarged saccule as shown by tomograph, the odds are 2 to 1 that they are enlarged bilaterally, and if not shown to be enlarged bilaterally by tomograph, may indicate a pathological condition.

The study of the laryngeal saccule is quite ancient. I quote from the footnote at the conclusion of Mr. Hilton's paper written in 1837.

"Sometime after I had forwarded for publication in our Hospital Reports, my paper on the laryngeal pouch with the drawings made from my own dissections, I received a note from Mr. James Babington, one of the editors, informing me that after perusing my paper he made a careful investigation regarding the laryngeal pouch and ascer-

tained that my description of it had been, in some measure, anticipated by Galen and Morgani and also by M. Gavart in a paper in the Journal de Physiologie."

When we are reminded that Giovanni Morgani died in 1771 and Galen in 210 A.D., how true is the saying, "There is nothing new under the sun." For the diagnosis of suspected pathology in the saccule, cultures, cell studies and tomographs would seem preferable because the thickness of the false cord prevents a satisfactory diagnostic biopsy. What we wish to emphasize again is the fact that underneath the false cord in many larynges, there is an enlarged cavity which potentially may develop a hidden pathological condition.

1100 NORTH CHARLES ST.

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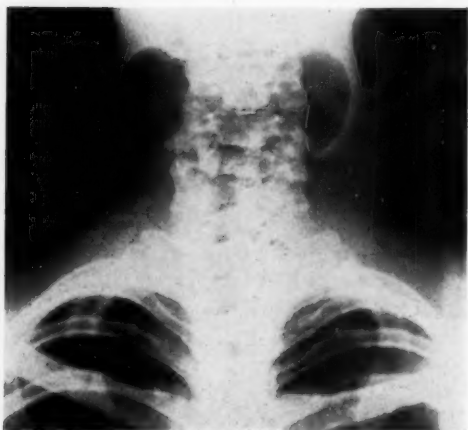
Fig. 1.—X-ray bilateral laryngoceles, anterior posterior view. Courtesy of Dr. Dudley C. Babb.

Fig. 2.—X-ray bilateral laryngoceles, lateral view. Courtesy of Dr. Dudley C. Babb.
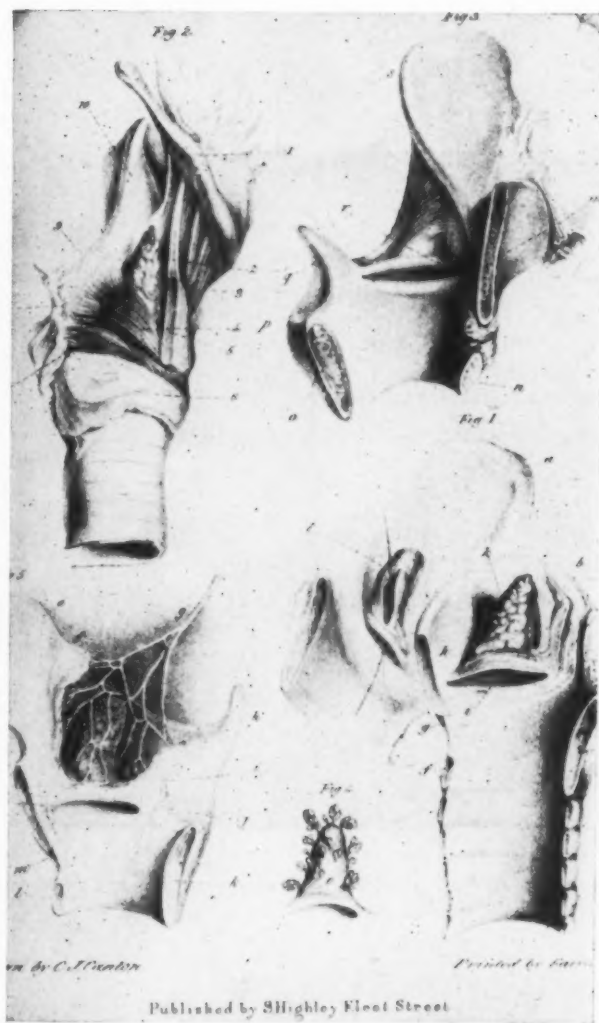
Fig. 3.—Drawings of the laryngeal saccule by Mr. Hilton.

Fig. 4.—X-ray pictures of an enlarged laryngeal saccule filled with cotton soaked in Lipiodol.

Fig. 5.—X-ray picture of an enlarged laryngeal saccule filled with cotton soaked in Lipiodol.

Fig. 6.—Bilateral enlarged saccules as shown by tomograph.

Fig. 7.—Microscopic section of an enlarged saccule.

Fig. 8.—Larynx by tomograph showing no enlarged saccules.

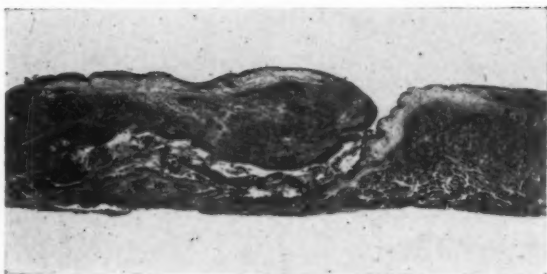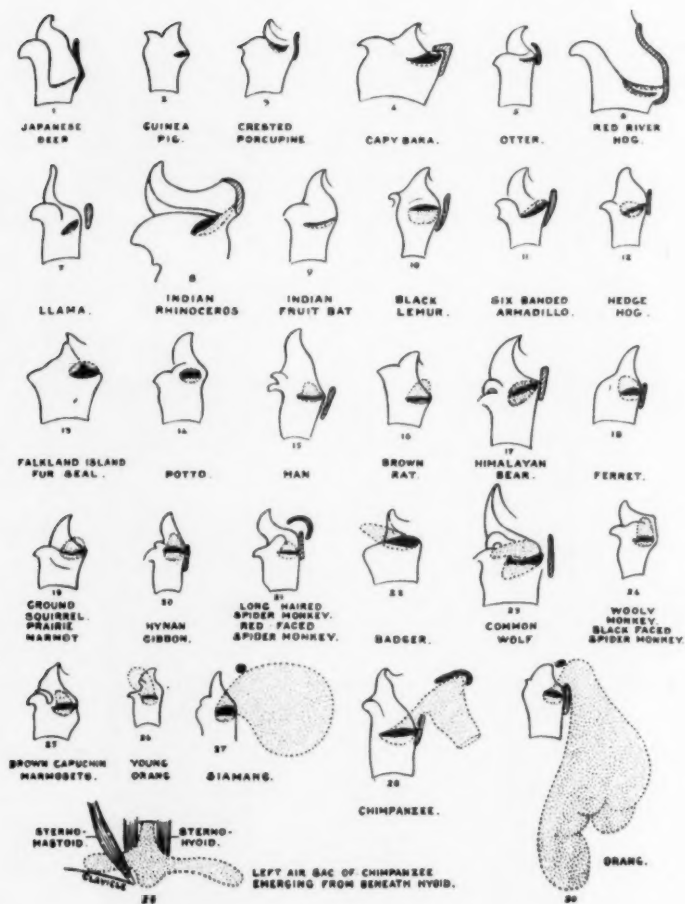Fig. 9.—Laryngeal saccules from Sir Victor Negus' "The Mechanism of the Larynx," (C. V. Mosby Co., St. Louis, by permission)

XXXIV

PSEUDOSARCOMA OF THE PHARYNX
AND LARYNX

Daniel C. Baker, Jr., M.D.

New York, N. Y.

Pseudosarcoma is the term introduced by Lane[1] to indicate the large polypoid connective tissue masses associated with squamous carcinoma of the mouth, fauces and larynx. He made a study of the pathological findings in ten cases. In the literature[2-4] the term carcinosarcoma is more commonly used to describe this type of relationship. Pseudosarcoma is a more suitable designation for the sarcoma-like masses because they are not malignant locally and do not metastasize. The important lesion is the underlying squamous cell carcinoma.

Not infrequently, the polypoid tumor mass of connective tissue will assume such prominence as to completely dominate the clinical picture. The lesion has the gross appearance of a sarcoma and when studied under the microscope, resembles a highly anaplastic growth with giant tumor cells. These factors can be misleading and may direct the attention of the laryngologist away from the underlying epithelial lesion, which is the true malignant tumor.

PATHOLOGY

The microscopic features of pseudosarcoma have been listed by Lane as follows:

1. The predominant tissue pattern shows a bizarre and mild appearance, usually with many giant cells.

2. In a few cases, cells and fibers form well fasciulated interlacing bands like fibrosarcoma.

3. In all cases, the general configuration and chromatin pattern of some nuclei were such as to cause a frankly atypical and anaplastic appearance.

4. The nature of the mitotic activity favored a malignant tumor.

Factors against a malignancy are:

1. Along with the atypical mitoses, abundant quite typical ones were noted.

2. A number of cells showed an apparent absence or inconspicuousness of the nucleoli.

3. Giant cells were very numerous.

4. The amount of edema and cellular inflammatory infiltrate suggested an inflammatory element.

5. Similar characteristic to the proliferative reparative cellular element of the granulating surface of a wound were observed.

The pseudosarcomatous tissue has a definite relationship to squamous cell carcinoma. In Lane's series, all showed squamous cell carcinoma. Three of his group had an intramucosal epithelioma, rather than invasive tumor.

Saphir and Vass[2] made a comprehensive study of 153 cases of carcinosarcoma reported in the literature. The following possibilities were considered, as an explanation of this relationship of the epithelial and connective tissue tumors. The lesion could represent a carcinoma growing into a benign connective tissue tumor; the inclusion of a benign epithelial tumor growing into a malignant connective tissue tumor; a chronic productive inflammation in the vicinity of an epithelial tumor; marked anaplasia; morphologic variation of tumor cells; and history and histologic evidence of x-ray irradiation. They concluded that the majority of cases reported as carcinosarcoma could be reconstructed as primary carcinoma. They thought that the spindle-shaped cells were probably transitional epithelial cells. Of the 153 cases, only three or four could be considered as true carcinosarcomas in which there was definite evidence of the malignant nature of both the epithelial and connective tissue element.

Frank and Lev[3] found that 48 per cent of all cases of carcinoma of the larynx showed some evidence of atypical arrangement of the epithelial cells. They concluded that carcinoma of the larynx shows great potentiality to show atypical sarcomatous arrangement of cells. They felt that the carcinoma showed the morphological variation rather than the connective tissue.

Pearlman,[4] in discussing carcinosarcoma of the esophagus, stated that the tumors were of uncertain histology and origin. The lesion was not a sarcoma but a foreign body reaction and that the true tumor was a squamous carcinoma.

Sims and Kirsch[5] reported two cases of spindle cell epithelioma simulating sarcoma in patients with chronic radiodermatitis. In one of the cases to be presented, there was a history of x-ray therapy to the local region where a pseudosarcoma eventually developed.

Bergman et al[6] reported a case of carcinosarcoma of the lung which showed a combined metastases of both the epithelial and sar-comatous tissue to a regional lymph node.

Stout, Humphreys and Rottenberg[7] reported a case of carcino-sarcoma of the esophagus in which the sarcomatous element was sug-gestive of rhabdomyosarcoma. The sarcomatous element metastasized independently to regional lymph nodes. The carcinomatous element was undifferentiated. In their case, it was an intermingling of both carcinoma and sarcoma and probably not similar to the cases referred to above.

Lane, on the basis of a review of the literature, as well as his own cases, believes that the carcinomatous component and not the sarcoma-tous element is the prime force in the majority of instances. The sar-comatous stroma is regarded as a secondary reactive phenomena and is interpreted as non-neoplastic. This element lacks autonomous metastatic capability and therefore the term pseudosarcoma is deemed appropriate and justifiable for the connective tissue proliferations in these cases.

REPORT OF CASES

CASE 1. D.D., a female, aged 51, was previously reported by Lane. She had received x-ray treatment to the right cervical region

for tuberculous lymphadenitis at the age of 15. She subsequently developed a squamous cell carcinoma and a basal cell carcinoma in the irradiated skin and which was treated by plastic surgery. Thirty years after x-ray therapy, a lateral pharyngotomy was performed for the removal of a pseudosarcoma and intramucosal epithelioma, involving the right aryepiglottic fold and right pyriform fossa. The patient remained well for six years and then developed an invasive squamous cell epithelioma in the same area. This was treated by total laryngectomy and partial pharyngectomy.

Her case is of interest because of the history of previous x-ray therapy in childhood. In the irradiated area, she developed a squamous cell carcinoma and basal cell epithelioma of the skin, and in the pharynx and larynx, a pseudosarcoma and intramucosal epithelioma, and finally 36 years after treatment, an invasive squamous cell carcinoma of the laryngopharynx. One must conclude that there was a relation between the x-ray therapy and the subsequent course of the patient.

CASE 2. T.W., a male, aged 58, was admitted to the hospital on May 23, 1957 with the history of hoarseness of six weeks' duration. Examination of his larynx showed the presence of a large pedunculated tumor attached to the anterior third of the left vocal cord and the anterior portion of the left ventricle. The tumor was about one and a half centimeters in diameter. The vocal cords showed good motility. There was no apparent ulceration. A direct laryngoscopy was performed and the polypoid mass was removed with cup forceps.

The examination of the tissue secured was reported by Dr. Lane as follows: "Sections reveal polypoid masses composed of exuberant fibrous and granulation tissue which is ulcerated over the surface. The fibrous component is made up of interlacing bundles of large plump, young fibroplastic cells, the nuclei of which exhibit varying degrees of atypism and occasional mitotic figures. Many of the nuclei are somewhat bizarre, hyperchromatic and contain large prominent nucleoli.

"Sections of a fourth fragment reveal loose edematous connective tissue partially covered by stratified squamous epithelium, and on one end of the section, a definite squamous cell epithelioma." It was impossible to determine whether this section represented an intramucosal epithelial change or a frankly invasive tumor.

On June 4, 1957, the larynx was opened by the laryngofissure route, splitting the thyroid cartilage in the midline. When the interior of the larynx was examined, it was obvious that the patient had an invasive tumor which involved the anterior part of the larynx from the left vocal cord upwards to the base of the epiglottis. A partial laryngectomy was performed removing all of the left vocal cord, both ventricular bands and the epiglottis, including the pre-epiglottic space. A foam rubber mold was left in the remaining portion of the larynx to maintain a lumen.

A study of the section of the tissue showed an invasive squamous cell carcinoma. The pathologist felt that the lesion was incompletely excised.

On June 18, 1957, a total laryngectomy and a left radical neck dissection were carried out. Examination of the specimen showed no evidence of carcinoma in any of the sections. However, it is believed that tumor tissue would have been found if every bit of the tissue could be examined. The patient has remained well.

Comment: In this case, the pedunculated tumor consisting of pseudosarcoma obscured the true nature of the patient's disease. He had an extensive squamous cell carcinoma. He would have been spared the partial laryngectomy had the extent of his disease been recognized.

CASE 3. S.T., a female, aged 44, was admitted to the hospital on December 5, 1955 with the history of severe attacks of dyspnea and choking spells for one year. The attacks of dyspnea were so severe that she would "black out." She was treated for bronchial asthma. Her attacks became increasingly severe and Dr. William Sherman, an allergist, was asked to see her, in consultation, at a hospital 50 miles from New York City. After his examination, Dr. Sherman did not believe that the patient had asthma, but that she was suffering from obstruction, either of the larynx or trachea. Her voice had been normal until a month before, at which time phonation was difficult because of her marked dyspnea. At Dr. Sherman's suggestion, a direct examination of the larynx and trachea was performed and a tumor mass was seen below the vocal cords. A tracheotomy was performed. The patient was transferred to the Presbyterian Hospital in New York City.

A direct laryngoscopy was done on the day after admission. A large reddish globular mass was found in the subglottic region. It was attached anteriorly and appeared to occlude the lumen. A biopsy was taken. The report of the biopsy was granuloma (pseudosarcoma type).

On September 12, 1955, a laryngofissure was performed and the tumor mass was found to measure 2.2 x 2 x 1.2 cms. The tumor was pedunculated and attached to the mucosa over the anterior part of the cricoid cartilage and to a small portion of the first two tracheal rings. It was possible to excise the mass including the attached portion of the cricoid cartilage and portions of the first two tracheal rings. After the tumor was removed, the lumen seemed adequate. A foam rubber mold was placed in the lumen and the wound was closed.

The report of the tissue by Dr. Lane was as follows: "Section revealed a connective tissue mass covered by stratified squamous epithelium with focal areas of ulceration. Focal areas reveal epithelial nests lying in the stroma. There is no cellular atypism. The stroma is composed of densely cellular interlacing bands of fibrous tissue and collagen fibers. Scattered throughout are many thin-walled blood vessels and diffuse acute and chronic inflammatory cell infiltration." Dr. Lane reported the lesion as a granuloma (pseudosarcoma type). He advised a very careful follow-up because of the possible relation of the lesion (pseudosarcoma) to squamous cell carcinoma. The patient has remained well for the past three and a half years.

Comment: This case is of interest in that an allergist was able to distinguish between status asthmaticus and laryngeal and tracheal obstruction. Fortunately for the patient, her problem was due to what is believed to be a benign tumor, pseudosarcoma without the presence of squamous cell epithelioma.

SUMMARY

Pseudosarcoma of the larynx and pharynx is a non-malignant connective tissue tumor, usually associated with squamous cell carcinoma.

The tumor may, by its size and location, obscure the true nature of the patient's disease.

Whenever a pedunculated tumor composed of connective tissue is found in the pharynx or larynx, the possibility of an underlying squamous cell carcinoma has to be considered.

903 PARK AVENUE

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XXXV

CYSTIC FIBROSIS OF THE PANCREAS
AND NASAL MUCOSA

Moses H. Lurie, M.D.
(By Invitation)

Boston, Mass.

Cystic fibrosis of the pancreas is a condition known to the pediatrician but a comparative stranger to the otolaryngologist. This disease has been recognized as an entity separate from celiac disease only in the past 20 years. That infectious and polypoid degeneration of the nasal mucosa is part of this condition has not been recognized by the otolaryngologist. Not only the nasal mucosa but the lung parenchyma may also be involved, and a great many of these cases have been treated for asthma, bronchiectases, severe allergy of the nose, or sinusitis. The disease also has been called mucoviscidosis on account of the abnormally viscid secretion from the submucosal glands of the respiratory and alimentary tracts.

Dorothy H. Andersen[1] in 1938 was the first to demonstrate that cystic fibrosis of the pancreas was a separate entity from celiac disease. She considered that it was due to one of three causes: 1) A congenital abnormality associated with atresia of the epithelial lined ducts of the pancreas. 2) Some inflammatory change during fetal life. 3) Or that it may be due to a Vitamin A deficiency.

The theory that the pathology of the pancreas was only one manifestation of an abnormality which affected all the mucous glands of the body was presented by Farber et al[2,3] in reporting his pathological findings from 1943-45. He found that all the mucous glands of the respiratory and alimentary tracts were involved. He also found that the mucous glands were distended and filled with inspissated material similar to that in the pancreas.

May and Lowe[4,5] in 1949 found marked variation in symptoms and intensity of the symptoms in the cases they studied. They felt that this condition appeared just before or after birth. They also felt that this condition was inherited and that the symptoms referable to the organ involved varied greatly in intensity and the progress of the disease was independent of outside factors. It is now believed that pancreatic insufficiency is not necessary to have this disease.

The pathological changes in cystic fibrosis involve the alimentary tracts and the respiratory tracts. As we are chiefly interested in the upper respiratory tract changes, little or no reference will be made to the intestinal tract symptoms.

Respiratory symptoms appear early: repeated colds, wheezing, blocked nose, a dry cough, bronchitis, bronchopneumonia, involvement of the nasopharyngeal mucosa, nasal mucosa, nasal sinus, and middle ear infections. A dry cough resembling whooping cough also may be present. Bronchiectasis may develop as a result of difficulty in getting rid of the thick mucoid discharge which is present in these cases. The nasal cavities may be filled with thick mucoid secretion, and polypoid changes may occur.[6]

The pathology present is an involvement of the submucosal glands. The glands are enlarged, distended and filled with secretion. The surface epithelium of the nasal cavity is of a normal type. This condition is not only present in the nasal mucosa but also extends into the paranasal sinuses causing a complete filling of the sinuses as reported by Dr. Pennington in 1956.[7] The nasal cavities when examined show turbinates with boggy purplish mucosa and a thick viscid mucopurulent discharge. Polyposis may occur in which the polyps present themselves in any part of the nasal cavity in the middle meatus region. The polyps when examined microscopically show chronic infection.

When the laryngologist sees young children presenting themselves with the symptoms of repeated infection either of the upper or lower respiratory system, a thick viscid discharge, nasal membranes not of boggy and allergic type but a purplish engorgement, cystic fibrosis of the pancreas should be ruled out. Polyps have been seen in the nose as early as the age of five.
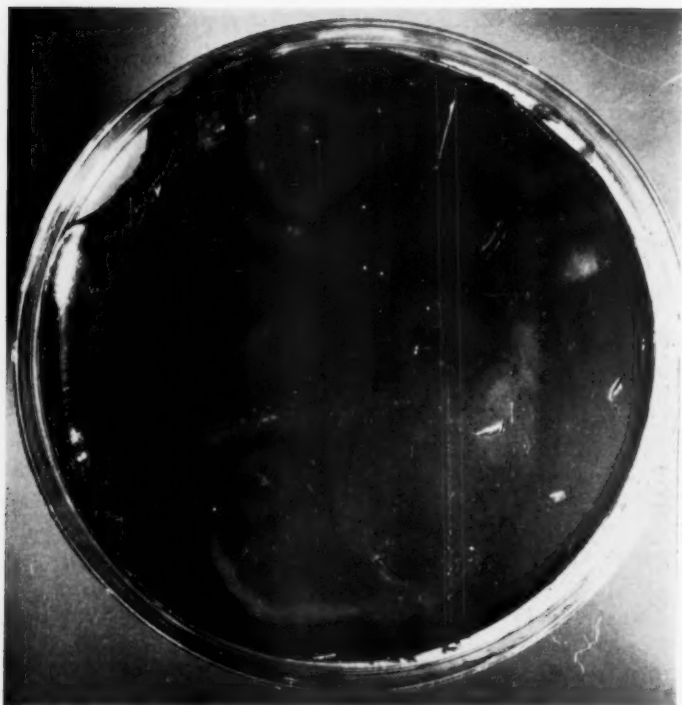
Fig. 1.—1 plus test. Negative test for cystic fibrosis.

The severe cases of cystic fibrosis are diagnosed very early by the pediatrician, but the mild cases may go for years without being recognized. The patient being treated for allergic infections of the sinuses and bronchial asthma without any benefit.

Cystic fibrosis gives a high concentration of sodium and potassium chloride in the perspiration of the patient. This has been reported by Darling et al.[8]

Shwachman and Gahm in 1956[9] reported a simple test for the detection of excessive chloride on the skin. This consists of placing

Fig. 2—3 plus test. Positive test for cystic fibrosis.

the patient's hand and fingers on a specially prepared agar medium which has in it a definite amount of silver nitrate and potassium chromate.

A high concentration of chlorides present will give an intense discoloration called 3 plus. One in between is called 2 plus and a minimum, 1 plus. Schwachman and Gahm reported that in 140 cases

of cystic fibrosis 138 of them gave a 3 plus impression, 2 gave a 2 plus impression, and none gave a 1 plus impression. In 77 normal children 65 gave a 1 plus result, 12 gave a 2 plus, and none gave a 3 plus test (Figs. 1 and 2).

They state that it is safe to presume that a patient with a 1 plus result does not have cystic fibrosis of the pancreas. Thus we have a simple test that will quickly eliminate noncystic fibrosis cases, and in border line cases the more quantitative sweat tests may have to be carried out.

If patients with these nasal symptoms are found to have a positive test, then the treatment of their nasal and sinus conditions should be put on an entirely different basis than that of pure bacterial infection or allergy. Operations on these cases to cure the condition are as a rule failures, and the patient may be subjected to repeated intranasal surgical interferences without any real permanent relief. To do radical surgery of the sinuses in these cases will give temporary relief of their symptoms; but as soon as the mucous membrane has regrown in the nasal sinuses, the basic pathology is again present.

The condition is treated from a pure symptomatic point of view. All these cases have secondary infections superimposed on the basic pathology. Cultures taken from the infected secretion should be made, and the appropriate antibiotic used. Autogenous vaccines have also been used.[10-12]

Nasal hygiene similar to that used in atrophic cases should be carried out. Polyps as they appear should be removed, and an adequate airway can be maintained by mild cauterization with 10 per cent silver nitrate or trichloracetic acid solution. Radical surgery need not be resorted to. In the cases that I have seen and followed over the past ten years, all have done well under this type of regime.

This condition may be found in several members of the same family; and when the diagnosis is made in one child, the other children of the family should be tested and examined for a question of cystic fibrosis.[13]

I would like to present three types of cases that have been seen with this condition.

1. In 1949 a five year old boy was seen on account of repeated colds, question of sinusitis, and an occasional attack of bronchial asthma. The nose showed thickened boggy turbinates congested but not pale as in allergy, moderately enlarged adenoid and tonsils not inflamed. Sinus x-rays showed thickened mucous membrane. A marked thick viscid secretion was present in the nose. The turbinates were cauterized with silver 10%, and he was put on a cocaine saline solution, one-fifth of 1%, to use as nasal drops.

A question of doing an adenoidectomy was considered. He improved slightly under treatment for about four months when a diagnosis of cystic fibrosis was made. With this diagnosis surgical interference was no longer considered, and he has been treated symptomatically for the past ten years. He is now 15 years of age. The nose and the sinuses have not changed during these years, but an adequate air space has been maintained by shrinkage and mild cauterization. The x-rays of his sinuses have shown no changes in the past eight years. They are filled with thickened mucous membrane. He now has bouts of asthma which are treated by the pediatrician. Infections present are controlled by antibiotics or sulfa drugs.

2. In 1945 a seven year old boy was seen with the complaint of vasomotor rhinitis. Examination showed a nasal mucosa with a polypoid tendency; color was that of passive congestion. The sinuses appeared slightly dark to transillumination. X-rays showed thickening of the mucosa of the sinuses.

Two years later he was brought in because of difficulty in breathing through his nose. The nose was found to be filled with polyps coming from the middle and inferior turbinates. These were removed under local anesthesia over a period of four months.

In 1950 a diagnosis of cystic fibrosis was made by Dr. Shwachman; and since then, he has been on small doses of aureomycin to control superimposed infection. His sinuses were filled with thickened membrane. He was also treated by cauterization and removal of polyps as they appeared. As he went through adolescence, it was noted that with control of superimposed infection, the polyposis was markedly less. At the present time, he appears about twice a year for removal of the same. Though his sinuses are still filled with thickened mucosa and superimposed infection, he has done very well.

He is now a senior in college. He now shows a definite minimal bronchial thickening of the right middle lobe of the lungs, suggesting bronchiectasis, otherwise negative.

3. The sister of the second patient was first seen in 1943 at the age of nine on account of marked polyposis filling both nares. The pediatrician reported that she had had pneumonia and bronchiectasis in January of that year. Previous to this, she had had a tonsillectomy, an adenoidectomy, and a question of an operation on the ethmoids to remove the polyps present.

Examination at this time showed a nose in which both sides were completely filled with polyps. The polyps filled the entire nose. The antra could be entered without difficulty. Intranasal opening may have been made at a previous operation; the middle turbinate could not be identified as such.

May, 1942, x-rays showed sinuses filled with thickened membrane. The lungs showed the upper third of the right lung with considerable diffuse infiltration extending well out toward the periphery. The appearance suggests tuberculosis. The remaining lung fields are clear.

In 1944, x-rays showed more infiltration of the lungs. Tuberculosis had been ruled out by tuberculin tests and repeated examinations of the sputum. During this period polyps were removed and a good breathing space obtained.

In 1948 at the age of 14, there was adequate breathing space in the nose, but there was still considerable mucopurulent discharge present. The patient was doing well.

In 1950 at the age of 16, she was still doing well although polyps had to be removed three or four times a year.

The pediatrician at this time made the following comment: "One is surprised to see an extremely well developed girl with extreme pulmonary disease for a long period."

At this time a diagnosis of cystic fibrosis was made by Dr. Shwachman, and the patient was put on terramycin. The polyps were

removed about twice a year. Since then, this girl has done very well and has graduated from college. She is now married. She has not been seen for two years for she is in Germany with her husband. Reports received state that she is doing well.

These three cases are more or less typical of the different types of pathology that can be seen in the nose from cystic fibrosis of the pancreas. All of them were treated symptomatically with satisfactory results. The problem is to make the diagnosis. This can be done with the simple sweat test. Patients with this type of disease should not be subjected to radical surgery of the sinuses as they will do better under conservative treatment.

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XXXVI

CAUSES OF FAILURE IN SURGICAL TREATMENT
OF MALIGNANT TUMORS OF THE LARYNX

Charles M. Norris, M.D.

Philadelphia, Pa.

In 1956, in a survey of 25 years' experience in the treatment of cancer of the larynx, Jackson, Blady, Norris and Robbins[4] reported end-results in a series of 695 cases treated by surgery or irradiation in the years 1930-1949. In this group were 210 cases treated by partial laryngectomy in which the five-year survival rate was 87% and 201 cases treated by laryngectomy with a five-year survival rate of 64%. The survival rates following initial surgical treatment had been increased to 91% and 67% respectively by subsequent treatment of recurrence or metastasis.

The present study includes an analysis of failures of surgical treatment in 209 determinate cases treated initially by partial laryngectomy (1940-1953), 181 determinate cases treated by laryngectomy without simultaneous radical neck dissection (1940-1953) and 64 cases treated by laryngectomy with simultaneous radical neck dissection (up to 1958). Patients previously treated by irradiation are included in the over-all group, but are also analyzed separately.

PREDISPOSING CAUSES OF FAILURE

In the broad sense, delays in diagnosis may be regarded as responsible for many of the surgical failures. Neglect of symptoms by the patient and casual or incomplete examination by the physician are encountered frequently.

To the laryngologist, problems in diagnosis should be infrequent. However, a study of cases has shown that delays may occur even in

the hands of the specialist as a result of one or more of the following factors: 1) careless examination of the larynx on indirect laryngoscopy, or failure to perform direct laryngoscopy when the mirror examination is unsatisfactory, 2) erroneous interpretation of the direct or indirect laryngoscopic findings, i.e., failure to recognize the indications for biopsy based on gross appearance, 3) inaccurate or insufficient removal of tissue for biopsy, usually as a result of faulty direct laryngoscopic technique, 4) inadequate follow-up in cases where a definite diagnosis is not established, or in cases where a pre-malignant lesion (such as leukoplakia) is found, and 5) failure to recognize the need for repeat biopsy because of false reassurance based on an initial negative biopsy. In the postoperative period, inadequate follow-up may result in late recognition of recurrence or metastasis, with loss of whatever chance for salvage remains.

TRENDS IN SURGICAL TREATMENT

In the past decade, two trends[5] have been apparent in surgery of cancer of the larynx. The first is the use of a wider variety of procedures in partial laryngectomy. Thus, while laryngofissure remains the standard procedure for localized invasive lesions of the middle third of the cord, the most frequently used procedure in our recent experience has been the fronto-lateral operation (Fig. 1), with removal of a vertical anterior segment of thyroid cartilage in continuity with the involved cord and ventricular band and the anterior extremity of the contralateral cord and ventricular band. An "extended" form of the fronto-lateral operation[9] with use of skin graft and mold, is useful in cases with a) posterior extension to or just beyond the tip of the vocal process, but not into the posterior commissure, b) beginning impairment of motion without actual fixation, c) limited and superficial extension to ventricle or margin of ventricular band or d) subglottic extension amounting to no more than a few millimeters. The frontal operation and the Alonso type of horizontal partial laryngectomy are satisfactory but less frequently used procedures.

The second trend is the increasing use of simultaneous radical neck dissection with laryngectomy, both in the presence of palpable metastasis and as an elective procedure for lesions arising in or extending to the subglottic or supraglottic regions or hypopharynx. Irradiation has proven of little or no value in controlling postopera-
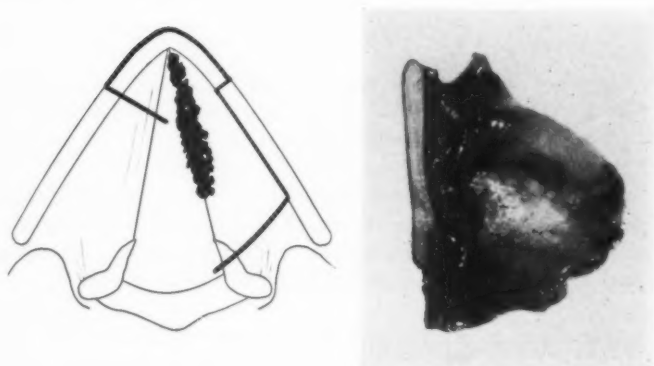
Fig. 1.—Frontolateral technique of partial laryngectomy. (a) Line of excision shown in horizontal plane at glottic level. (b) Typical specimen showing anterior vertical segment of thyroid cartilage and anterior extremities of contralateral cord and ventricular band in continuity with entire involved cord and portion of ventricular band. This technique is preferred to laryngofissure for lesions closely approaching or involving the anterior commissure.

tive metastases. The present study substantiates the observations of others as to the useful role of the elective procedure.

CLASSIFICATION AND SELECTION OF TREATMENT

Pending general adoption of a uniform system of clinical stage classification, cases in the present study have been placed in five categories, as follows:

1. *Endolaryngeal.* Lesions arising on the vocal cord, with or without extension into the ventricle, but not extending above the margin of the ventricular band or to the arytenoid.

2. *Subglottic.* Including both lesions of subglottic origin and those which have extended from the cordal level into the subglottic region. Lesions involving only the under surface of the cord are not included in this group.

3. *Vestibular.*   Lesions arising on the lower half of the epiglottis or on the ventricular band, or extending from the cord to involve these regions.

4. *Marginal.* Lesions involving the upper half of the epiglottis, the ary-epiglottic fold or the arytenoid, whether by origin or by extension from the cordal or vestibular areas.

5. *Hypopharyngeal.*   Lesions arising in the pyriform sinus or postcricoid area are included in the study because of frequent involvement of the posterior or lateral portion of the larynx with problems in surgical treatment similar to those of the larynx proper.

Superficial cordal lesions, including carcinoma-in-situ, and those in which a pre-existing leukoplakia has undergone beginning malignant alteration have seemed to be curable by irradiation in a high percentage of cases, providing cordal motility is not impaired.   Other cordal lesions without appreciable impairment of motility and small lesions of the upper portion of the epiglottis may be treated by the various forms of partial laryngectomy.   All other lesions are treated by laryngectomy, with or without radical neck dissection depending on the location of the primary involvement.

Careful evaluation of the lesion is directly related to success or failure.   Motility is best determined by indirect laryngoscopy.   At the time of direct laryngoscopy, the use of forward and right-angle telescopes, by providing a magnified image above, at or below the glottis, may help in evaluating the gross extent of the lesion.   Plani-

graphic study and occasionally mucosography may be useful in determining the degree of subglottic extension.   In vestibular and anterior marginal lesions, extension toward the base of the tongue may be indicated by widening of the vallecula, or by palpation of the lingual tonsillar area.

FAILURES OF PARTIAL LARYNGECTOMY

In the years 1940-1953, partial laryngectomy was used in 247 cases, of which 225 (91.1%) were followed.   Excluding 16 patients who died of unrelated causes without evidence of local recurrence or metastasis within five years, 209 cases remain for analysis.

TABLE I

TREATMENT OF RECURRENCES FOLLOWING
PARTIAL LARYNGECTOMY—15 CASES

	TOTAL CASES	DETER-MINATE	DEAD OF DISEASE	5-YEAR SURVIVALS
2nd partial	1	1	0	1
2nd partial - LG - X-ray - ND	1	1	0	1
LG	6	5	0	5
LGND - Contralateral ND	1	1	0	1
LG - X-ray	1	1	1	0
Irradiation only	3	2	1	1
Untreated or treated elsewhere	2	1	1	0
Totals	15	12	3	9

(LG = laryngectomy ND = radical neck dissection)

Of the 26 cases (12.4%) classed as failures, 15 (7.2%) developed recurrence within five years, 5 (2.4%) developed metastasis without local recurrence, 4 died of carcinoma of the lung (primary or metastatic) and 2 (1.0%) were postoperative deaths (one cardiac decompensation and one cardiac or air-way obstruction).

Recurrence was found at intervals of 3 months to 4 years 11 months, with an average interval of 20 months; however, 8 (53%) of the recurrences were found within the first year. The subsequent treatment in the 15 cases of recurrence is detailed in Table I. Nine of the patients treated for recurrence have survived for five years or more, thus increasing the survival rate following the initial operation (183/209 or 87.6%) to 192/209 or 91.9%.

Of the five patients developing metastasis following partial laryngectomy, none survived. Three were returned for further treatment. In one of these, metastasis without local recurrence appeared in two months, but complete removal of metastatic disease by radical neck dissection was impossible because of extension deep about the subclavian vessels. In another case, in which an Alonso operation and

simultaneous right neck dissection had been previously performed, death following contralateral neck dissection was the result of post-operative cardiac decompensation and aspiration pneumonitis. A third patient was treated by irradiation because of cervical spine metastasis in addition to lymph node metastasis, and died in less than three months.

Histologic grading of the cases in which recurrence or metastasis occurred following partial laryngectomy showed nothing distinctive. Two cases were of well-differentiated squamous cell carcinoma and 18 were moderately well differentiated. There were no cases of undifferentiated carcinoma in this group.

FAILURES OF LARYNGECTOMY

In the years 1940-1953 laryngectomy without neck dissection was used in 217 cases, of whom 197 (90.8%) were followed. Excluding 16 cases in which death within five years was due to unrelated causes, without evidence of recurrence or metastasis, 181 cases remain for analysis. Cases in which previous partial laryngectomy had been performed are excluded from the series, but those previously treated by irradiation are included.

The years studied represent a period during which simultaneous radical neck dissection was being used increasingly with laryngectomy, but in which the overall majority of cases not suitable for irradiation or partial laryngectomy were treated by laryngectomy alone (except for those in which metastases were palpable).

Sixty-nine cases (38%) of the group of 181 are classed as failures of laryngectomy, 21 (11.6%) having had recurrence as the first clinical manifestation of failure, 37 (20.4%) having had cervical metastasis alone and 6 (3.3%) having had recurrence with metastasis observed concurrently. Four patients died of carcinoma of the lung (primary or metastatic). Two patients had signs of brain metastasis in addition to regional node metastasis. There was one operative death (cardiac arrest in a patient with complete heart block), but no post-operative deaths occurred in this group.

In Table II the location of lesions according to the above classification is related to the incidence of recurrence or metastasis. Recur-

TABLE II

LARYNGECTOMY WITHOUT RADICAL NECK DISSECTION (1940-1953)

Location of Lesions Related to Incidence of Failures of Initial Operation in
181 Determinate Cases Without Palpable Metastases Before Operation

	DETER-MINATE	RECUR-RENCE	METAS-TASIS	REC. AND METASTASIS	FAILURES
Endolaryngeal	52	1 (2%)	3 (6%)	1	5 (9.6%)
Subglottic	50	8 (16%)	8 (16%)	1	17 (34%)
Vestibular	49	7 (14%)	14 (29%)	0	21 (43%)
Marginal	26	3 (12%)	11 (42%)	4	18 (69%)
Hypopharynx	4	2 (50%)	1 (25%)	0	3 (75%)
Totals	181	21 (11%)	37 (20%)	6	64 (35.3%)

rence occurred with about equal frequency in the subglottic and vestibular groups (16% and 14.3% respectively). In four of the lesions classified as vestibular, some subglottic involvement was also noted. The frequency in marginal lesions (11.5%) was somewhat smaller. Recurrence following laryngectomy for endolaryngeal carcinoma was noted in only 1 of 52 cases (2%). The average interval prior to clinical detection of recurrence was 1.2 years, but in only two of the 21 cases was the interval longer than two years. Multicentric origin was noted in only one case, but might possibly have been found by careful microscopic study in others.

In 7 of the 12 cases in which recurrence was associated with subglottic involvement (including the four vestibular cases extending below the glottis) the first indication of residual disease was induration adjacent to the tracheal stoma or compression of the trachea a short distance within the stoma. It is felt that these cases may represent metastasis to pre- or paratracheal nodes or to thyroid gland, rather than actual "recurrence" due to inadequate excision of the lesion. Ogura[10] and Ormerod[12] have recently emphasized the importance of this lymphatic route.

As described by Rouviere,[17] the infra-glottic lymph-collecting trunks of the anterior group pass 1) through the cricothyroid mem-

brane to the prelaryngeal node or nodes, and thence to the pre- and paratracheal nodes, or 2) directly to the deep cervical nodes. The lateroposterior trunks of the infraglottic group pass directly to the paratracheal nodes on either side (Fig. 2), and thence to the inferior deep cervical nodes. As Ogura[10] has pointed out, removal of the paratracheal nodes cannot be well accomplished without inclusion of the corresponding thyroid lobe. Furthermore, in his comprehensive study of surgical specimens, Ogura has found embolic malignant cells in lymphatics within the thyroid gland, as well as the more generally recognized direct extension.

Adequate surgery in subglottic cases would appear to require inclusion of a generous segment of the upper trachea (usually more than would be though necessary below the gross lower border of the mucosal lesion) in continuity with the isthmus and thyroid lobe on the involved or most involved side. If the pharynx is entered initially at the vallecular level, and the larynx freed from above downward, upward traction may then facilitate inclusion of a more adequate segment of upper trachea, as well as liberation of the inferior portion of the thyroid lobe.

Seven of the 21 patients with recurrence alone were treated by irradiation (including three found non-resectable) and died. Two of 8 cases in which resection of recurrence was done have survived without evidence of disease for more than five years.

Postoperative metastasis to deep cervical nodes, without concurrent evidence of recurrence, was most common in the marginal cases (42.3%). The incidence was somewhat smaller in the vestibular group (28.6%) and in the subglottic group (16.0%), but the latter does not include the cases mentioned above in which recurrence may actually have been paratracheal or thyroid metastasis. Metastasis following laryngectomy for endolaryngeal carcinoma was noted in only 3 of 52 cases (5.8%), and 2 of these were salvaged for five years or more by secondary radical neck dissection. It would thus appear that elective neck dissection should be of importance in all categories except for the endolaryngeal.

Kuhn et al[7] found lymph node metastasis in a still higher percentage of vestibular and marginal cases (43.4 and 78.6%, respectively). The postoperative interval before appearance of metastasis

TABLE III

TREATMENT OF METASTASES FOLLOWING LARYNGECTOMY
(37 Cases)

			FIVE YEAR SALVAGE
No treatment	6		0
Failed to return		3	
Refused operation		1	
Concom. pul. metast.		2	
Inoperable	5		0
On clinical examination		3	
On exploration		2	
Surgery elsewhere	2		0
Neck dissection (unilateral)	18		7
Neck dissection (bilateral)	3		0
X-ray alone or post-op.	11		0
			7 (19%)

varied from one month to three years, but in only two of the 37 cases was the interval longer than two years.

Secondary radical neck dissection for postoperative metastasis was done in 20 of the 37 cases. Two were considered inoperable on exploration. In the remaining 18, unilateral neck dissection was completed and 7 of these (39% or 19% of the group of metastases) have survived five years. Clerf[3] reports a five-year survival of 36 (32%) of 113 patients treated for postoperative metastasis by secondary neck dissection. Radon implantation was used at the time of operation in two of the seven cases surviving. None of the three cases in which staged bilateral neck dissection was performed for palpable metastasis survived. Of the 7 apparently cured by secondary neck dissection, 2 were in the endolaryngeal group, with 4 in the vestibular group and one in the marginal group. The methods of treatment and end-results in cases with postoperative metastasis are summarized in Table III.

None of the 6 cases of subglottic lesions developing metastasis were salvaged by neck dissection, perhaps because of the greater predilection
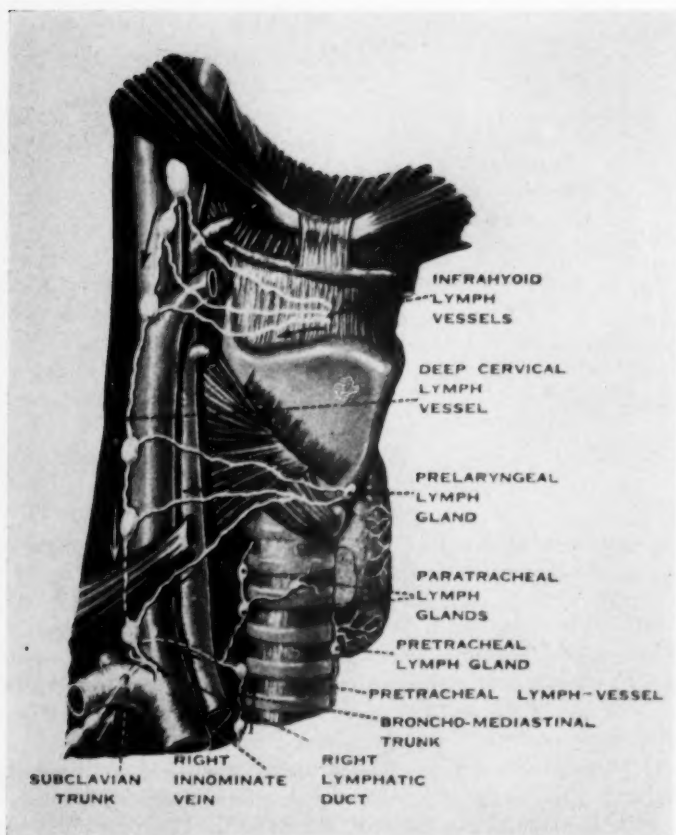
Fig. 2.—Lymphatic pathways from the larynx (from Hamilton, W. J., Textbook of Human Anatomy, MacMillan and Co., Ltd., New York, 1957). In the case of subglottic lesions, the relations of the infraglottic drainage to prelaryngeal, pretracheal, paratracheal and deep cervical nodes is of importance (see text).

for involvement of the inferior deep cervical nodes (Fig. 2), which are not only more difficult to palpate when small, but more difficult to remove completely by neck dissection.

Data relating degree of malignancy to incidence of recurrence and metastasis are given in Table IV. Except for the fact that frequency of metastasis in the moderately well differentiated lesions is appreciably greater than that from well differentiated lesions, grading based on initial biopsy appears in this study to have limited prognostic value, particularly since variations in degree of malignancy are often found in different parts of the same tumor. Kuhn et al[7] found that cervical node metastasis occurred in none of 12 cases of Grade I carcinoma and in 70% of 20 cases of Grade IV.

TABLE IV

LARYNGECTOMY WITHOUT RADICAL NECK DISSECTION (1940-1953)

Histologic Grading Related to Incidence of Failure of Initial Operation
in 181 Determinate Cases of Squamous Cell Carcinoma

	CASES	RECURRENCE	METASTASIS	FAILURES
Well differentiated	24	3 (12.5%)	3 (12.5%)	6 (25%)
Mod. well differentiated	153	22 (14.4%)	33 (21.6%)	55 (35%)
Undifferentiated	4	2 (50%)	1 (25%)	3 (75%)

The over-all salvage in the 64 patients developing recurrence or metastasis following laryngectomy was small (nine cases or 14%). Two of 27 patients with recurrence and 7 of the 37 with postoperative metastasis have survived five years or more following secondary surgery. Partial justification for the poor salvage rate may lie in the fact that many of the patients lived at distances so great as to make return for follow-up seem impractical; some of these were returned for further treatment (if at all) only when recurrences or metastases had reached an advanced stage. Inclusion of the cases salvaged raises the five-year survival rate for laryngectomy from 112/181 (62%) to 121/181 (67%).

SIMULTANEOUS LARYNGECTOMY AND
RADICAL NECK DISSECTION

Simultaneous laryngectomy and radical neck dissection has been the initial form of surgical treatment in 64 cases (up to 1958). Two patients are unfollowed and 5 died of unrelated causes without evidence of residual disease. In the remaining group of 57 cases, simultaneous neck dissection was done for palpable nodes in 41 and as an elective procedure in 16. Microscopically positive nodes were found in 6 (37.5%) of the 16 cases of elective neck dissection.

Among the 57 cases, which of course do not qualify for five-year end-results, and which include a disproportionate number (eighteen) of hypopharyngeal cases, there have been 22 failures to date. Twenty of the 22 failures have been in cases with palpable nodes which were positive on section.

Only one case of six in which nodes were not palpable but were positive on section is a failure to date, and only one case of 16 in which the nodes were reported negative (6 palpable, 10 not palpable) has been a failure. Putney[13] found that in a group of 62 cases of simultaneous elective neck dissection the incidence of positive nodes was 16 (26%); 12 of the 16 patients were free of disease for from 2 to 6 years.

In the 20 failures with palpable positive nodes in our series, failure was due to recurrence in 5 (3 of which were hypopharyngeal lesions), recurrent metastasis in 5 (3 of which had had simultaneous bilateral dissection) and uncontrolled contralateral metastasis in 7 (4 of which were bilateral marginal lesions). In 2 cases death was due to carcinoma of the lung, and in 1 metastasis to the cervical spine occurred.

Of particular interest are the cases in which contralateral palpable metastasis developed following simultaneous laryngectomy with unilateral neck dissection. Subsequent contralateral metastasis occurred in 8 (25%) of 32 cases in which the laryngeal lesion had been unilateral; one of these was vestibular, three were marginal and 4 were hypopharyngeal. Metastasis to the second side occurred in 14 (56%) of 25 cases in which the laryngeal lesion was bilateral; of the 14, 2 were subglottic, 4 vestibular, 5 marginal and 3 hypopharyngeal.

Considering unilateral and bilateral cases together, metastasis to the contralateral or second side occurred in 2/7 (29%) of the sub-

glottic cases, 5/12 (38%) of the vestibular cases, 8/19 (42%) of the marginal cases and 7/18 (39%) of the hypopharyngeal cases.

SURGICAL TREATMENT AFTER IRRADIATION

The frequent difficulty of proving residual or recurrent carcinoma following irradiation, due to concomitant perichondritis and edema is well known. Despite this, prognosis does not appear to have been affected to any significant degree in cases in this study previously treated by irradiation. Seven of the 209 determinate cases of partial laryngectomy (1940-1953) had previously had x-ray therapy, and in this group there was only one failure, a recurrence, in a patient who was not returned for further treatment and died following further irradiation.

Twenty-two of the 181 determinate cases of laryngectomy without neck dissection had previously had courses of irradiation. Twelve of the 22 cases required no further treatment after laryngectomy and survived without evidence of disease from 5 to 17 years. In two other cases (one with metastasis and one with recurrence) a five-year salvage was obtained by further surgery. Seven patients died of disease without further treatment and one died of other cause (coronary) after 1½ years. The overall five-year survival rate, including salvage, for this group is 64%, only slightly less than the corresponding figure (67%) for the entire group treated by laryngectomy.

The incidence of recurrence in this group was somewhat higher (6/22 or 27%) than in the entire laryngectomy group (12%), but the frequency of metastasis without recurrence was lower (2/22 or 9% as compared to 20%). Leroux-Robert[8] is of the opinion that "radiotherapy is of at least as much prophylactic value as radical neck dissection," and employs routine postoperative irradiation in vestibular carcinoma without palpable nodes. Trible[15] feels that instances in which an inoperable lesion is rendered operable by irradiation are rare.

ASSOCIATED CARCINOMA OF THE LARYNX AND LUNG

Carcinoma of the lung was observed concurrently or subsequently in 15 cases of carcinoma of the larynx treated surgically (1940-1953). To determine with certainly whether these were pri-

mary or metastatic from the larynx has, as in the experience of others,[2,14] been difficult. As Cahan points out, the only valid criterion of independent primary origin is a different histologic type. In seven of the cases (2 of recurrence following laryngectomy, 3 of cervical node metastasis following laryngectomy and 2 in which laryngectomy and radical neck dissection had shown positive nodes), the interval to the appearance of the pulmonary lesions was less than six months. These might logically be assumed to be metastatic, the probable route being by way of the cervical lymphatics, subclavian or innominate veins, vena cava, right heart and pulmonary artery.

In the other 8 cases, also considered as failures in the above analysis, death due to the pulmonary lesions ensued without recurrence or metastasis in the neck after an interval of 1 to 8 years. The lung carcinoma in these cases may have been primary, since metastasis to the lung would seem unusual without cervical node metastasis or recurrence. In two cases of this group, multiple nodules suggestive of hematogenous metastasis were found on the chest x-ray, but in the remaining six a single tumor-like density was found in 4 and lobar atelectasis in 2. Three of these 6 lesions involved the right upper lobe, 2 the left upper lobe and 1 the left lower lobe. Despite the theoretical possibility that mucosal implantation may occur, the distribution of these lesions does not favor such a hypothesis.

Auerbach[1] has demonstrated the occurrence of multiple foci of carcinoma-in-situ and actual invasive carcinoma in the tracheobronchial tree in autopsy cases of bronchogenic carcinoma. It might be speculated that this multicentric potential occurs in the entire lower respiratory tract. Thomson and Schaff[14] in reporting a series of 20 autopsy cases of carcinoma of the larynx, 5 of which also showed bronchial carcinoma, conclude that cancer of the larynx and bronchus in the same patient should be regarded as separate primary tumors and treatment given on this basis. In our statistics, however, all cases in which carcinoma of the lung occurred have been considered as failures of surgical treatment.

SURGICAL TREATMENT IN UNCOMMON MALIGNANT TUMORS OF THE LARYNX

Data regarding surgical treatment of tumors other than squamous cell carcinoma are given in Table V. Two of the four patients with

TABLE V

SURGICAL TREATMENT IN UNCOMMON MALIGNANT TUMORS OF THE LARYNX

PATIENT	TYPE	LOCATION	TREATMENT	RESULT
f 37	Adenoid cystic carcinoma (cylindroma)	Subglottic	Partial Laryngectomy	N. E. D. 5½ yrs.
f 64	same	Epiglottis	Partial Horiz. Laryngectomy (Alonso)	N. E. D. 4½ yrs.
m 45	same	Right ventricle	Partial Laryngectomy	Rec. and pul. met. 6 yrs. Local excision - lobectomy Further multiple pul. met. LWD 12 yrs. from 1st op.
m 61	same	Left ventricle	Laryngectomy	Concurrent rib. met. (same histology) CNS met within 2 mo. DOD
m 63	Fibrosarcoma	Ant. ¾ right cord	Partial LG (fronto-lateral)	N. E. D. 14 months
f 65	same	Ant. third each cord	Laryngofissure ant. commissure	N. E. D. 9 years
f 66	same	Mid. third right cord	Laryngofissure clipping tech.	N. E. D. 4½ years
f 14	same	Right ventricle	Partial LG	Recurrence 10 months LG NED 2 years
m 59	Neurogenic sarcoma	Ant. half right cord	Laryngofissure ant. commissure	Recurrence 3 months LG - recurrence 2 mo. Wide excision - rec. 3 mo. Radon implantation DOD 11 months

LG = Laryngectomy NED = No evidence of disease

LWD = Living with disease DOD = Dead of disease

adenoid cystic carcinoma are living and free of disease after four and a half and five and a half years, one having been treated by partial laryngectomy with excision of a portion of the subglottic area, and one following an Alonso operation. The two other patients in this group developed distant metastases without cervical node metastasis. In one case, lobectomy was done for a solitary lesion which proved to be of identical histologic picture; although multiple metastatic nodules

Fig. 3.—Unpredictable prognosis in carcinoma of larynx. *Top*: Unusually extensive squamous cell carcinoma of larynx (almost completely destroyed) and hypopharynx, with deep invasion of base of tongue. Laryngectomy, subtotal hypopharyngectomy and partial glossectomy with right radical neck dissection. No evidence of recurrence or metastasis five years after left radical neck dissection. Hypopharynx has been reconstructed by tube pedicle grafts (Dr. John V. Blady). *Bottom*: Endolaryngeal squamous cell carcinoma grade II, with fixation of left cord, treated by laryngectomy without radical neck dissection. Metastasis appeared in the left inferior deep cervical nodes in less than four months. Left radical neck dissection; death from recurrent cervical and pulmonary metastasis in eight months.

appeared in the lungs, shortly after lobectomy, the patient is active and essentially asymptomatic after six years. In the other case, death appeared to be due to central nervous system metastasis soon after laryngectomy. This patient also had metastasis to rib, proven by biopsy to be of the same histolotic type as the laryngeal primary.

In 4 cases of fibrosarcoma (3 of which were in females) there are 3 survivors without evidence of disease following partial laryngectomy, the intervals being 14 months, $4\frac{1}{2}$ years and 9 years. Laryngectomy for recurrence was required in the remaining case, a female of 14 years, but no evidence of recurrence or metastasis has developed after nearly two years.

One additional case of sarcoma, thought by the pathologist to be of the neurogenic variety, demonstrated the presumed tendency for local spread along lymphatics of the nerve sheaths, since multiple recurrent nodules were observed locally, first after laryngofissure, then after laryngectomy, then after wide excision of recurrence in and about the tracheal stoma with radon implantation. Death occurred less than two years after the initial operation.

Johnston[6] in a recent report of 3 cases of fibrosarcoma of the larynx, found irradiation to be an unsatisfactory method of treatment. His review of previously reported cases showed that metastasis to lymph nodes and distant areas rarely occurs from this type of tumor.

COMMENT

As in cancer of other organs, prognosis in carcinoma of the larynx may be quite unpredictable (Fig. 3). However, improvement in end-results may be achieved only by analysis of failures as well as successes, and application of relevant conclusions to selection of treatment and surgical technique.

There appears to be little question that partial laryngectomy will retain its present useful place in surgical treatment. The availability of a wider variety of techniques is expected to increase the field of application of conservative procedures in limited lesions of the endolarynx and, to a lesser degree, the epiglottis. Thus, of 16 cases treated by the "extended frontolateral" technique and recently reported,[9]
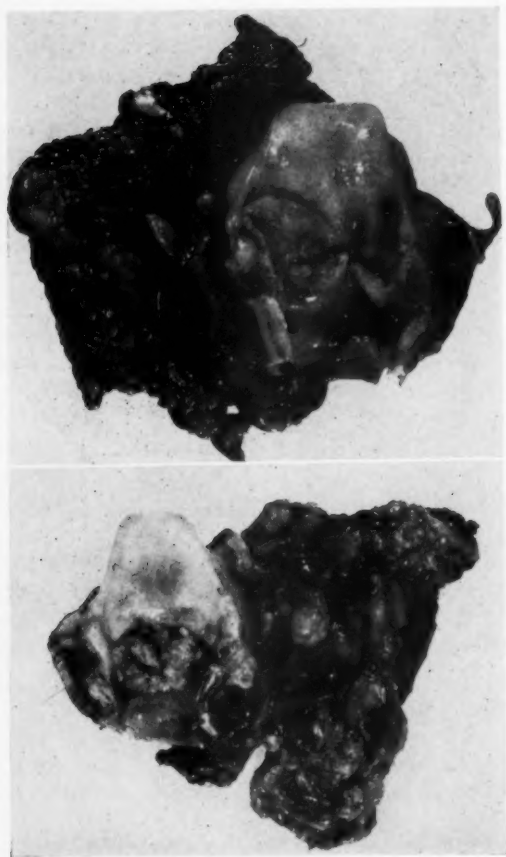
Fig. 4.—Simultaneous laryngectomy and radical neck dissection. *Top*: Unilateral cordal and vestibular lesion requiring laryngectomy and simultaneous radical neck dissection, whether nodes are palpable or not. In this case, nodes were not palpable, but were positive on microscopic examination. *Bottom*: Bilateral cordal and subglottic lesion. Laryngectomy and radical neck dissection on side of palpable nodes (microscopy positive). Elective radical neck dissection on second side will usually be indicated, even though nodes are not palpable. Metastatic nodes from subglottic lesions are frequently in the inferior deep cervical group, where early detection by palpation is difficult, and the prospect of complete extirpation, once nodes become palpable, is poor.

14 (87.5%) required no further treatment and are apparently free of disease from 3 to 7 years.

Obviously a faulty estimate of the extent of the lesion is largely responsible for recurrence following partial laryngectomy. Extension beneath the mucosal surface may be difficult to evaluate by gross inspection. Thirteen of the recurrences were in cases of laryngofissure (10 by the clipping technique and 3 by the anterior commissure technique) ; one each followed the frontolateral and extended frontolateral operations. A review of these cases suggests that in some instances of laryngofissure, where the lesion was found to approach the anterior commissure more closely than had been anticipated, the frontolateral operation might have been safer (Fig. 1).

The most important points in technique of partial laryngectomy appear to be adequate initial surgical exposure of the lesion through tissues known to be uninvolved, and unhurried excision, with good visualization of the margin of apparently normal tissue at all times.

The high frequency of postoperative metastasis following laryngectomy, and the relatively high incidence of nonpalpable but microscopically positive nodes in cases of simultaneous laryngectomy and neck dissection appear to apply to all locations except the endolaryngeal. This of course suggests that, as others have advocated, the use of laryngectomy without neck dissection should be confined to endolaryngeal lesions not suitable for treatment by irradiation or partial laryngectomy. Although Ogura[10] favors elective neck dissection even in these cases, the fact that metastasis occurred in only 3 ot 52 endolaryngeal lesions in our series, and the fact that 2 of these 3 cases with postoperative metastasis were salvaged, raises some question as to the necessity for such an approach. However, the routine removal of thyroid isthmus and lobe, along with an additional segment of upper trachea, as advocated by Ogura, appears to be a sound method of avoiding postoperative recurrence in the pre- and paratracheal areas.

In the presence of proven carcinoma of the larynx, palpable nodes along the deep cervical chain should be considered to be metastatic, without need for further proof by needle biopsy or excision biopsy, since a negative result cannot be regarded as conclusive, and since the latter method involves some risk of dissemination.

Since in the case of bilateral lesions involving other areas than the endolaryngeal, metastasis to the second side (following unilateral neck dissection) occurred with an incidence of 56%, staged bilateral neck dissection should usually be advocated in these instances, whether or not nodes are palpable on the second side. Simultaneous bilateral neck dissection is not favored because of the increased morbidity (and probable increased mortality) resulting from simultaneous bilateral internal jugular vein ligation. Simultaneous bilateral dissection with ligation of only one internal jugular may fail to achieve adequate removal of nodes.

In the vestibular and anterior marginal cases, where extension to the pre-epiglottic space occurs frequently, the hyoid bone should always be included with the specimen, and the intact thyrohyoid membrane along with the overlying ribbon muscle should also be included. In predominantly unilateral lesions of the marginal or hypopharyngeal type, the pharynx should be entered through the contralateral pyriform sinus, so that the lesion may be evaluated by inspection and palpation before the line of excision is carried through the base of the tongue and along the hypopharyngeal wall on the involved side.

SUMMARY AND CONCLUSIONS

1. Failures of surgical treatment of squamous cell carcinoma of the larynx have been studied in 209 determinate cases of partial laryngectomy, 181 determinate cases of laryngectomy without radical neck dissection and 64 cases of laryngectomy with simultaneous neck dissection.

2. In the 209 cases with initial surgical treatment by partial laryngectomy, the incidence of failures due to recurrence was 7.2% and that due to metastasis was 2.4%. Nine of 15 patients with recurrence were salvaged, 8 by further operation and 1 by irradiation. The application of the several available techniques of partial laryngectomy is discussed as an important aspect of the continued usefulness of conservative surgical treatment in suitable cases.

3. In the 181 cases with initial surgical treatment by laryngectomy without simultaneous neck dissection the incidence of recurrence within five years was 11.6% and that of cervical node metastasis without recurrence was 20.4%. Some of the "recurrences" adjacent

to the tracheal stoma were undoubtedly thyroid, pre- or paratracheal metastases.

4. Postoperative metastasis following laryngectomy without neck dissection was studied in relation to location of the laryngeal lesion, and was found to occur in 6% of the endolaryngeal, 16% of the subglottic, 29% of the vestibular and 42% of the marginal cases. Only seven of 37 patients with postoperative metastasis were salvaged by secondary radical neck dissection.

5. Twenty of a group of 22 cases of simultaneous laryngectomy and neck dissection, in which nodes were not palpable but microscopically positive, or were microscopically negative (6 palpable, 10 not palpable) are living with no evidence of disease from 1 to 8 years. Of the 16 patients in this group operated more than three years ago, 14 (87.5%) are apparently free of disease, 4 having had contralateral neck dissections 6, 5½, 2½ and 2 years ago. The lesions represented in this group of sixteen included 4 subglottic, 5 vestibular, 5 marginal, and 2 hypopharynx.

6. In addition to the generally accepted view requiring simultaneous radical neck dissection in the presence of palpable movable nodes, the data from this study support the proposals of other authors that laryngectomy with elective radical neck dissection is indicated for subglottic, vestibular, marginal and hypopharyngeal lesions without palpable nodes(except for limited lesions of the upper portion of the epiglottis suitable for treatment by horizontal partial laryngectomy of the Alonso type). In the case of bilateral lesions in these locations, staged bilateral radical neck dissection would appear usually indicated.

7. Previous treatment by irradiation had little effect on survival rates following treatment by partial or total laryngectomy.

8. Surgical treatment and end-results in nine cases of uncommon malignant tumors of the larynx are briefly reviewed.

TEMPLE UNIVERSITY MEDICAL CENTER

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XXXVII

HISTOCHEMICAL STUDIES OF THE
PATHOGENESIS OF
NASAL POLYPS

ALEX WEISSKOPF, M.D.

AND

HELEN F. BURN, M.S.
(By Invitation)

SAN FRANCISCO, CALIF.

The etiology of the nasal polyp, a source of considerable specula-
tion since the Hippocratic era, is still very much open to discussion.
The literature has presented a gamut of pathogenesis, ranging from
tumor through infection and allergy. An excellent review of the
historical background was made by Berdal[1] in 1954. In recent years,
the generally accepted opinion has been that the polyps are on an
allergic basis, particularly the perennial types, such as perennial aller-
gic rhinitis and asthma.[2-8] On the other hand, there has been consid-
erable evidence to show that bacterial infection could be a major
factor in causing nasal polyposis.[9-13] To complete the cycle, it must
be mentioned that even viruses have been implicated, although this
has not been proved.[14]

Discussion necessarily has been speculative since previous histo-
logic and biochemical studies were limited by inadequate facilities.
New methods for the study of connective tissue have been devised in
the last ten years. Semenov,[4] in a classical review of allergy in diseases
of the nose and sinuses, related allergy to the collagen diseases. With
great intuition, he questioned the fate of the connective-tissue ground

substance and related it to the myxomatous changes seen in the nasal and sinus membranes following allergic inflammation. Rawlins[15] likewise discussed with perception the importance of the connective-tissue mesenchyme. He suggested that changes in the mesenchymal ground substance are reflected in inflammatory changes of the respiratory tract.

In a previous study by Weisskopf and Burn in 1958,[16] the background of the work on connective-tissue ground substance was reviewed. Changes in the ground substance, both normal and pathologic, were discussed and were related to nasal function and disease. The similarity of response of ground substance and nasal mucous membranes was presented as a theoretical basis for further understanding of nasal physiology. The present work on nasal polyps is a continuation of this study.

METHODS

Twenty-three patients were studied, including 17 with allergic polyps, three with infectious polyps, and three with abnormal mucous membranes from the maxillary sinus. The polyps were obtained from routine cold-snare polypectomies and the mucous membranes by the Caldwell-Luc procedure. Cocaine and epinephrine were used for anesthesia. The anesthetics, such as Pontocaine® or Cyclaine®, which do not shrink the tissue, did not give sufficient room within the nose for proper visualization. The technique was identical to the work previously reported except for the fact that 1000 turbidity reducing units of hyaluronidase (Wydase®) were used instead of 500 as in the previous study. It was felt that the excess amount would insure complete depolymerization of the acid mucopolysaccharides present.

The slides were run in groups; one incubated in buffered saline, the second in testicular hyaluronidase, and the third in bacterial hyaluronidase, for 90 minutes at 37 degrees C. Three stains were used after incubation: toluidine blue, Rinehart and Abul-Haj colloidal iron, and periodic acid-Schiff.

The findings in the 23 cases were consistent; no more patients were considered necessary. The infectious polyps were differentiated from the allergic by the presence of frank purulent infection, unilateral polyposis, and the lack of a definite history of allergy. This is an

arbitrary separation which has been used by other authors.[9,11] The attempt to differentiate allergic from infectious polyps was felt to be of more than academic interest. Variation in the connective-tissue reaction to allergy as differentiated from bacterial inflammation would not only be of considerable significance in understanding polyp formation, but also might clarify the reaction of connective tissue to these traumata. The Caldwell-Luc specimens consisted of two cases of bacterial sinusitis and one antral cyst. These were included to study the reaction of the sinus mucosa since this is an important site of polyp formation.

The pitfalls of histochemical studies were kept in mind. It must be emphasized again that the variations described in the study of the nasal turbinates[16] were also seen in the polyps. The amount of ground substance often varied markedly in the same polyp. The connective-tissue cells, likewise, ran the gamut from very primitive mesenchymal cells to mature fibrocytes. Inflammatory cells varied from area to area so that the total picture must be grasped before the tissue reaction can be interpreted. This emphasized the need for continued enzymatic control of the sections to ascertain that what was seen was actually acid mucopolysaccharide. Secondly, the continued use of sections of umbilical cord as a control of the staining reaction was most important. By its use, changes in tissue reaction can be traced to staining artifacts or to those which may actually be due to disease. The umbilical cord is a rich source of acid mucopolysaccharides. In one instance, several polyps showed an unusual staining reaction to the colloidal iron stain while the umbilical cord stained at the same time showed normal characteristics. It was felt that these tissues, which had been obtained by other surgeons, might not have been placed in fixative immediately, thus causing these alterations.

RESULTS

Hematoxylin and Eosin Stain. Routine hematoxylin and eosin sections were not unusual. There was little difference between the infectious and the allergic polyps except for the type of inflammatory cells. The infectious polyps showed a greater percentage of round cells, primarily plasma cells with some lymphocytes. However, eosinophiles were readily found and this was felt to be an uncertain method of differentiation.
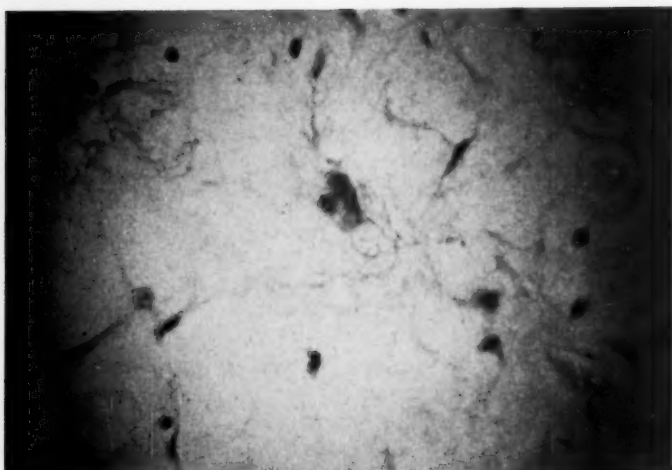
Fig. 1.—(H & E, 43X)   Polyp. Myxoid stroma.   Fibroblasts in several
stages of maturation.

All of the polyps were covered with respiratory epithelium and
occasional areas of stratification.   No metaplasia was seen.   Goblet
cells were varied and showed no consistency of response.   The base-
ment membrane was not consistently present.   When present, it was
thinner than in normal turbinates.   In many of the polyps there was
no demonstrable basement membrane.   The cellular infiltration and
capillaries of the lamina propria thus abutted the cells of the epitheli-
um.   The polyps were of the edematous myxomatous type except in
two patients who had a preponderance of collagenous tissue.   Both
of these patients had a definite history of allergy.   The usual histologic
variations were included in the predominant myxomatous group.
There were large inclusion cyts lined with squamous or cuboidal
cells.   Some were lined with a respiratory type of ciliated epithelium
and goblet cells.   In the loose areolar tissue, many cystic areas were
seen which were apparently empty or filled with fine granular and
fibrillar amorphous material.

With the hematoxylin and eosin stain, the predominant cell
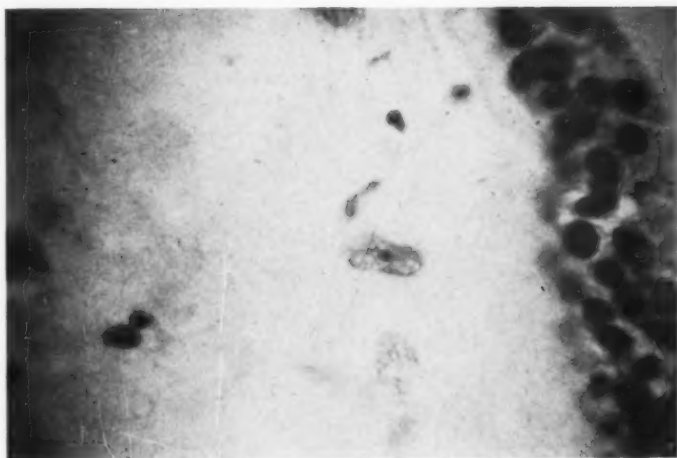was the fibrocyte, or more mature fibroblast, which is fusiform

Fig. 2.—(H & E, 97X) Primitive fibroblast or mesenchymal cell. Characteristic reticular nucleus and dense nucleolus. Note absence of definite basement membrane.

(Fig. 1). The cytoplasm stained poorly so that the cell was seen with difficulty. The nucleus tended to contain densely staining chromatin material with no definite nucleolus. Scattered throughout were the usual inflammatory cells consisting of plasma cells, small lymphocytes, eosinophiles, and rarely polymorphonuclear neutrophiles. The cells were concentrated primarily beneath the epithelium and about the blood vessels. The blood supply originated in the pedicle. At first the arterioles were thick-walled and muscular, but as they branched through the polyp, the wall of the vessel became thinner and less cellular. Finally, the capillary, whose wall was a single endothelial cell, was formed, ending in a capillary loop adjacent to or in the basement membrane. This frequently was only large enough to permit the passage of one or two red blood cells. Associated with the blood vessel was the so-called primitive mesenchymal cell. These cells were apparent on sections stained with hematoxylin and eosin because of their large, loosely reticulated nuclei containing large, densely staining nucleoli. They were found throughout the polyp wherever capillaries were present and were especially noteworthy
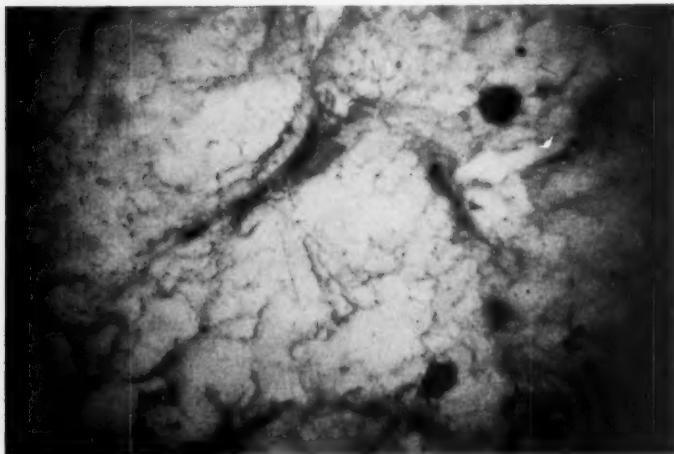
Fig. 3.—(Colloidal iron, 97X)   Fibrillar precipitation of ground sub-
stance in the edematous cyst.   This is concentrated particularly about the
stellate fibroblasts.

where evidence of tissue activity and reaction were present, such as
granulation tissue and fibroplasia.   The importance of these cells will
be discussed below when correlated with the histochemical findings
(Fig. 2).

Histochemical Findings.   Histochemical techniques presented the
polyp in a different light.   Histochemical stains revealed the error of
interpreting slides stained with hematoxylin and eosin.   In several
cases, the basement membrane which had seemed to stain with hema-
toxylin and eosin, turned out to be a dense, collagenous infiltration
with very little of the acid mucopolysaccharides which are a constant
component of the basement membrane.   The false basement mem-
brane appeared to be a condensation of the fibrillar collagenous ma-
terial of the normal basement membrane.   Conversely, where no
basement membrane could be seen after staining with hematoxylin and
eosin, there occasionally was some increase in the amount of acid
mucopolysaccharides with the colloidal-iron stain.   It must be pointed
out that in the nasal polyp, analysis of the basement membrane is

probably not very helpful since the polyps arise from an area of the
nose and sinuses where basement membrane normally is vestigial.[4]   In
the turbinates, loss of basement membrane was reported consistently
in the allergic state.[17]   The exact site of origin of these polyps was
not recorded at the time of operation.   No further information
regarding the epithelial cells was derived from the histochemical
studies.   The usual positive response of the mucopolysaccharide of the
mucus was present.   This was not removed with hyaluronidase and
was consistent with previous findings.

The amorphous, eosinophilic, fibrillar material of the edematous
cyst showed evidence of blue-staining mucopolysaccharides inter-
spersed with proteinaceous material.   In others, the same eosinophilic
material became intensely blue with colloidal iron or metachromatic
with toluidine blue stains.   There was a certain consistency in these
findings.   The acid mucopolysaccharide appeared to be more dilute or
depolymerized as the areolar structure became looser.   In the cystic
spaces, its presence was shown by fine blue fibrils interspersed with
the red-staining collagenous fibrils and the green cytoplasmic processes
of the fibroblast.   The concentration of ground substance mucopoly-
saccharides increased about the blood vessels and became extremely
heavy in areas showing tissue activity.   There was a direct relation
between the amount of mucopolysaccharides and the number of
capillaries and large mesenchymal primitive fibroblasts (Fig. 3).

On the other hand, mast cells which were fairly frequent in
normal nasal tissues were relatively infrequent in the polyp.   This
was in disagreement with Baglioni and Leonardelli[18] who reported
these as "seen quite frequently."   The mast cells increased in number
about areas of capillary activity, but there was no correlation between
the number of mast cells and the mucopolysaccharides present.   This
was further evidence that the mast cell is not directly connected with
the formation of mucopolysaccharides.   Of more than passing interest
was the discovery that many of the mast cells showed evidence of
locomotion.   The looseness of the polyp tissue revealed the unre-
stricted cell so that pseudopodia were seen (Fig. 4).

The primitive mesenchymal cells described above with the hema-
toxylin and eosin stain were consistently associated with increased
ground substance.   It was possible to predict areas of increased
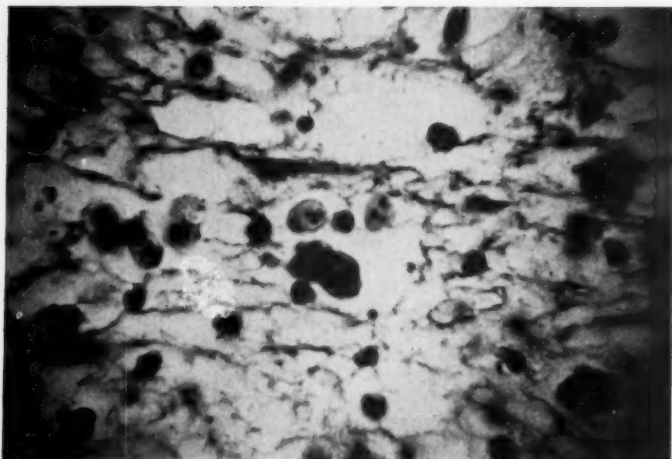ground substance from the hematoxylin and eosin sections by noting

Fig. 4.—(Colloidal iron, 97X)   Mast cell showing pseudopod.   Areolar arrangement consists of fine pink-staining collagenous fibrils with adherent mucopolysaccharides.

the increased numbers of these young cells.   Increased ground sub-stance was also found in and around the endothelial cells of the blood vessels.   The small capillaries showed this especially well.   The endo-thelial cells were readily visible, unhampered by the presence of other cells or connective-tissue elements.   The consistency of this finding must be emphasized.

There are conflicting reports in the literature as to the source of the ground substance about vessels.   The fact that the mucopoly-saccharides were within the endothelium adds weight to the theory that the endothelial cells are an active factor in the formation, or at least accumulation, of ground substance.   Curran[19] has shown by means of autoradiographs that there was a pronounced uptake of radioactive S^{35} by endothelial cells associated with the presence of sulfated acid mucopolysaccharides.

The most useful stain for studying these changes was the col-loidal iron since it detected even the more depolymerized acid muco-

polysaccharide as seen by the blue-staining colloidal iron and meta-chromasia as shown by toluidine blue. As the intensity of blue increased, indicating greater concentration and greater polymerization of ground substance, the metachromasia increased. The fact that metachromatic material was present, even in areas which are not normally metachromatic, was shown nicely in the polyp pedicle which had been crushed by the cold snare. In this concentrated area, meta-chromasia was present.

The fact that the ground substance was composed of acid muco-polysaccharides was proved consistently by using hyaluronidase. Metachromasia was almost completely lost by treating with bacterial hyaluronidase, and there was some loss in the blue-staining colloidal iron. The testicular hyaluronidase (Wydase®) will remove all the metachromasia and practically all the remaining colloidal iron-staining material except for a minimal amount. The colloidal iron-staining material in the capillary endothelium was particularly resistant to the hyaluronidase. This indicated that the mucopolysaccharides of the ground substance consisted of both hyaluronic acid and the chon-droitin sulfate complex. Complete lack of removal from the endo-thelium indicated that this mucopolysaccharide was probably of the heparin, chondroitin sulfate B type.

The most dramatic increase in ground substance was found in the infectious polyp in which there was much more evidence of cellular activity. It must be pointed out, however, that the same increase in mucopolysaccharide could be found in scattered puddles in the allergic polyp where evidence of tissue reaction was present, with increase in vascularity and fibroplasia. Thus the amount of mucopoly-saccharide was not related to infection or allergy, but was related to the activity of the tissues.

That this activity does not have to reach the magnitude of granu-lation tissue was seen especially well in one section. With hematoxy-lin and eosin stain, it appeared to be an edematous, areolar type of polyp; however, the toluidine blue stain showed it was filled with a concentration of ground substance sufficient to be metachromatic. The predominant connective-tissue cells were the young stellate fibro-blasts. These cells appeared to be directly related to the primitive mesenchymal cells described earlier. The nucleus was large, reticu-lated and contained a prominent nucleolus. The cytoplasm indicated
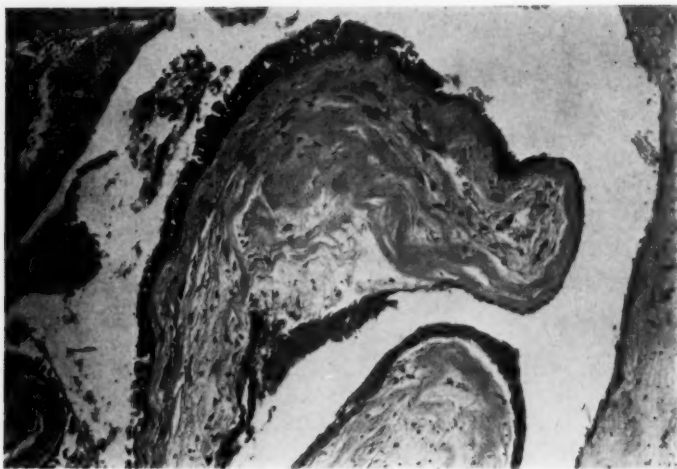
Fig. 5.—(H & E, 10X) Sinus mucosa from antral cyst. Edema and amorphous infiltration. The primary cell of the stroma is the large primitive fibroblast.

its increased maturation by the stellate process and associated fibrils. These processes frequently meshed with adjacent cells to form the areolar network of the polyp.

It is generally accepted that most polyps originate from the mucous membrane of the sinuses and the meati. With this in mind, three cases of antral mucosa obtained from Caldwell-Luc procedures were studied. One was from a patient with an antral "cyst" who had a history of mild allergic symptoms. Each of the other two patients had a frank, infectious sinusitis. One was a chronic case of long standing, the other an acute, relatively new case of three months' duration which was caused by a hemolytic staphylococcus. It was of interest to note that in all three cases there were areas of loose areolar, edematous tissue indistinguishable from the ordinary nasal polyp. The consistent cell types were the plasma and lymphocyte, the infectious cases showing formation of lymph follicles with secondary centers. Eosinophiles were present but were not predominant.

There was a distinct difference between the acute and chronic sinusitis. In the chronic case, there was dense collagenous fibrosis, but even here, the acid mucopolysaccharide was ubiquitous, being in and around the collagenous tissue as well as scattered about the blood vessels and in the areolar areas as previously described. On the other hand, the acutely infected tissue, which was likewise extremely thick and polypoid, showed an extensive infiltration of cells masking the underlying edema. There were many areas of new capillary formation, typical of granulation tissue. There were also the usual cystic areolar spaces. The histochemical stains gave evidence of a tremendous accumulation of mucopolysaccharide. There were large areas of metachromasia. The colloidal iron stain was so heavy that it masked the cells, even in the cystic areas. The heaviest concentration was seen in areas which showed new capillary formation and the presence of the large, foamy fibroblasts in the hematoxylin and eosin stain.

The antral cyst likewise showed areas of edematous, loose areolar tissue. Nothing remarkable had been seen with the hematoxylin and eosin stain except that on close study the presence of many, very large cells with loose reticular nuclei were seen, similar to the large primitive fibroblasts described before, but larger and more reticulated. These cells appeared to be associated constantly with dense, eosinophilic fibrinoid material (Fig. 5). The histochemical stains presented a very dramatic picture of remarkable infiltration of mucopolysaccharides. There was extensive metachromasia. The colloidal iron stain showed large pools of almost pure mucopolysaccharide lying in polypoid fingers of the antral mucosa. The areas of positive stain were associated with these large primitive cells. Of particular interest is the fact that the cells were not necessarily close to blood vessels or new capillary formation. It would appear that these cells were related to the mucopolysaccharides (Fig. 6).

The Schiff stain was studied but has not been discussed since it was so nonspecific. It has been reported to react positively with mucopolysaccharides, glycogen, mucoproteins, glycoproteins, collagen, gelatin and reticulin, among other substances. The results of the polyp study were in agreement with this, since much more of the tissue stained positively with Schiff than with the toluidine blue or the colloidal iron. Enzymatic action with the hyaluronidases did not significantly change the picture, giving further proof that the Schiff reaction depends upon other components than the acid muco-
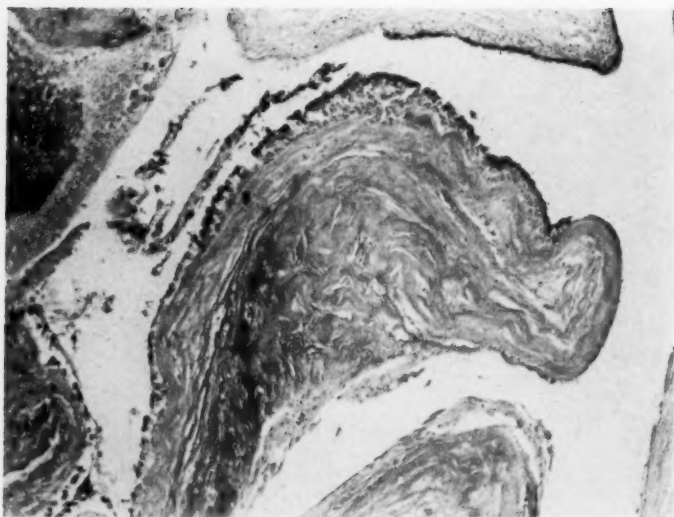
Fig. 6.—(Colloidal iron, 10X)   Same area as Figure 5.   The amorphous
filtrate is now seen to be a dense accumulation of acid mucopolysaccharides,
which stains an intense blue and is removed with hyaluronidase.

polysaccharides.   Of interest in passing, however, is the fact that
many fibroblasts contained fine Schiff-positive red granules which
were not seen in the other stains.   Occasionally the colloidal iron
stain showed a fibroblast with fine, blue granules in the cytoplasm.
This may be the precursor of the ground substance.   There is insuffi-
cient evidence for more than speculation at the present time.

COMMENT

The present study revealed the following significant findings
which are helpful in understanding the pathogenesis of polyps.

1. The similarity between the allergic and the infectious polyp
in cellular response, structure, and presence of acid mucopolysac-
charides in the ground substance presents further evidence that the
connective-tissue response is identical in both cases.   In the past few
years it has become more and more evident that allergy is an inflam-

matory reaction of the connective tissue similar to other inflammatory reactions. Semenov[4] calls allergy "the great imitator." The common denominator "inflammation" is a non-specific reaction, whether due to antigenic, bacterial, chemical, viral or mechanical insults.[15,20-23]

2. There was an increase in the amount of acid mucopolysaccharide as compared to the normal nasal mucosa. The amount of ground substance was directly related to the amount of tissue reaction as evidenced by the presence of tissue mesenchymal cells and immature fibroblasts. The polyp is thus seen as an active progressive growth due to reaction of the connective tissue, rather than due to the mechanical engorgement of extravasated edema fluid. The chronic allergic polyp which has developed over a long period of time shows the least amount of ground substance. The mucous membranes from the antra suggest that the source of the polyp is an active center of formation of the mucopolysaccharide as shown by the intense metachromasia and colloidal-iron reaction.

3. The relationship between the ground substance, the endothelial cells, and the primitive fibroblasts was most striking. The proximity of the mucopolysaccharide hints that these cells may well be the source of the ground substance or at least intimately connected with its formation. These cells are typical of the mesenchymal cells described in embryonic and healing tissues. Reference to these cells associated with ground substance has not been found in the literature. This probably has not been observed before because most tissue is so dense that differentiating the individual cellular elements is difficult, if not impossible. The polyp is a most favorable tissue in which to observe the individual cells since they lie in a loose, unimpeded stroma.

4. No direct relationship was observed between the other cellular elements and the ground substance. Mast cells were noted but scattered so that a definite search had to be made to find them. This is in contrast to the normal nasal mucosa which showed mast cells in almost every field of the "high-dry" objective. This appears to be further evidence that the mast cells are not directly related to the formation of the ground substance, at least in the nose.

The nasal polyp has been found to be a most useful tissue for the study of connective tissue reactions and related ground substance. Its loose areolar structure makes the identification of the cells relatively simple and makes possible the exact localization of areas to

compare enzymatic changes. In fact, the polyp could be considered as a tissue culture, *in vivo*. Further studies on the cytologic and ground substance responses to various agents including the hormones are in progress.

SUMMARY

1. A review of the literature reveals that the pathogenesis of the nasal polyp is still a puzzle, although many theories have been introduced.

2. Twenty-three patients were studied, 17 with allergic polyps, three with infectious polyps, and three with abnormal mucous membranes from the maxillary sinus.

3. Histochemical studies revealed:

a. The constant presence of acid mucopolysaccharide ground substance in all the polypoid tissue, even in the so-called edematous cyst.

b. An increased amount of ground substance with increased tissue activity as evidenced by increase in primitive fibroblasts and capillaries.

c. Evidence that the primitive fibroblast or mesenchymal cell, as well as the endothelial cell, is active in the formation of the ground substance.

4. The presence of active connective tissue elements, both cellular and stromal, suggests that the polyp is more than edematous nasal mucosa. It appears to be a connective-tissue response to chronic stress of the nasal membranes.

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XXXVIII

WEGENER'S GRANULOMATOSIS

JOSEPH P. ATKINS, M.D.

AND

SYLVAN H. EISMAN, M.D.
(by invitation)

PHILADELPHIA, PA.

Wegener's granulomatosis is a disease which has been recognized since 1931, when Klinger[1] first described it. In 1936, Wegener[2] first described and characterized it as a syndrome consisting first of necrotizing granulomata of the upper or lower respiratory tract; second, generalized necrotizing vasculitis involving arteries and veins, almost always involving the lungs; and third, renal decompensation, almost always leading to terminal uremia and death.

The number of reported cases is rapidly increasing, but we have been unable to find references to this disease in the American otolaryngologic literature, though several reports are available in the British literature.[3,4] It seems important that this disease should be recognized by the otolaryngologist and broncho-esophagologist, because it frequently presents initially as a problem involving the upper or lower respiratory tract. A further purpose of this paper is to point out several instances of granulomatous lesions involving the respiratory tract which cannot be distinguished clinically from the onset symptoms of Wegener's granulomatosis, but which do not follow the unfavorable course which characterizes most cases of Wegener's granulomatosis. Without being able to settle the matter, it seems proper to raise the question as to whether or not benign forms of this disease exist or if treatment in these non-fatal cases has been fortuitously successful in arresting the progress of the disease.

The etiology of this disease is unknown, though some authors have considered it a variation of polyarteritis nodosa.[3,5-8] Cambier[9] speaks of Wegener's syndrome as the respiratory form of polyarteritis nodosa. It seems reasonable to classify Wegner's granulomatosis with the group of diffuse collagen diseases. Many have suspected that an element of hypersensitivity exists,[10,22] but it has been remarkable that the usual manifestation of hypersensitivity, such as eosinophilia, urticaria, and bronchospasm have been generally absent. It has also been suggested that drug sensitivity may be related to this condition,[11] but many cases have been reported in which no medication had been used prior to the onset of the disease. No constant bacterial invaders have been recognized. Walton[12] suggests that the respiratory lesions are primary and the wide spread lesions occur later in the natural history of the disease, these secondary lesions being due to hypersensitivity reaction to a drug or tissue breakdown product. The non-fatal cases reported below could represent situations in which the secondary lesions failed to appear.

The pathological features of this disease have been analyzed by Fahey[13] and his co-workers and by Godman and Churg[10] in their excellent papers where they analyze seven cases. Four of the seven exhibited destructive necrotizing granulomatous lesions in the upper respiratory tract, characterized by the presence of granulation tissue, giant cells, foci of necrosis and inflamed small vessels. Necrotizing giant cell granulomas were present in the lungs and bronchi of all cases. Circumscribed nodules of active or healed pulmonary vasculitis were present in every case. The kidneys showed focal necrotizing thrombotic glomerulonephritis, more or less wide spread. In the subacute phase, these lesions showed a tendency to heal by capsular epithelial proliferation and granuloma formation. Focal granulomas were also encountered in the renal interstitium, often periglomerular in location. There was splenic involvement in all cases, ranging from small foci of necrosis to total infarction. Vascular lesions of other organs occurred less frequently, as well as scattered focal granulomatous lesions which were often frankly necrotic and usually contained giant cells. Other organs involved have been the esophagus,[13] the eye,[14] and the skin.[12]

Skin lesions are being recognized more and more as a frequent manifestation of the disease. These are by no means specific or characteristic; they may well reflect the vascular lesions presenting areas

of focal necrosis and even gangrene. Where cutaneous lesions occur, it should be borne in mind that histologic examination of these areas is more likely to demonstrate a significant pathologic configuration than will be obtained in the airway, where moisture and secondary bacterial invasion cloud the picture.

The differential diagnosis[15] must attempt to separate this syndrome from similar and related disease patterns of necrotizing granulomatous processes, generalized arteritides, as well as mixed allergic angiitis and granulomatosis. One, therefore, separates the following lesions:

1. Specific infectious granulomatous disease, such as syphilis and tuberculosis.

2. Lethal midline granuloma,[16-18] malignant granuloma, idiopathic lethal granuloma, and malignant granuloma of the nose are terms describing a disease which involves the midline tissues of the nose in a progressive, ulcerating granuloma, associated with crusting, bleeding, deep ulceration, and usually a fatal outcome. It is similar to Wegener's granulomatosis in that there is a granulomatous involvement of the nasal area. This disease also has been thought to have a relationship to polyarteritis nodosa,[19,20,23] but in no reported case has there been evidence of death by renal failure, though Williams[18] reported renal impairment in one case. The granulomatous lesions have not shown the vasculitis which characterizes Wegener's granulomatosis. Death in this disease is by its local destructive effects rather than by its systemic disturbance.

3. Boeck's sarcoid may sometimes involve vessel walls, but it is non-necrotizing and does not produce glomerulitis.

4. Classical polyarteritis nodosa involves principally medium sized arteries, and also involves both arteries and veins of all organ systems, though one rarely if ever sees necrotizing granulomata of the respiratory tract. In polyarteritis nodosa, an allergic history and eosinophilia are quite common, but these are not necessarily a part of the picture of Wegener's granulomatosis. Hypertention, too, is much more common in polyarteritis nodosa. Lesions within the pulmonary parenchyma may be seen in polyarteritis nodosa, but rarely do they give the appearance of bronchogenic carcinoma. Joint symptoms are

much more common in polyarteritis nodosa than in Wegener's granulomatosis.

5. Granulomatous or vascular lesions may be found in certain patients who present clinical evidence of an allergy. Loeffler's syndrome may fall into this class. The vascular lesions here are demonstrated in the lungs, but are not generalized.

Wegener's granulomatosis may be distinguished on the basis of: a) marked predominance of necrotizing granulomatous lesions in the respiratory tract and their aggressive nature, b) the regular occurrence and severity of the renal lesions, c) the relative absence of clinical stigmata of allergy or tissue eosinophilia. The significance of recognition of this disorder in the past has been only academic, but with the development of steroid therapy and possibly chemotherapy such as cytotoxic agents and x-ray therapy, one may hope to prevent or at least postpone the renal failure that uniformly leads to death in periods of a few weeks or months.

We should like to present case reports of several patients with this process and refer to others who may well represent examples of this condition, though the terminal features at the time of this report have fortunately not yet appeared.

REPORT OF CASES OF WEGENER'S GRANULOMATOSIS

CASE 1. W.L., aged 48 years, white male. The patient was admitted to the Hospital of the University of Pennsylvania on March 9, 1958 for investigation and treatment of sores on the left arm and back. Except for recurrent otitis media, bilateral, since childhood, he was in his usual health until December, 1957, when he developed a "pimple" on the left forearm; this later discharged thick, creamy pus. It continued to drain for one month, and he finally visited his personal physician in January, 1958. Local treatment was prescribed, but the lesion persisted. In mid January, he developed a sore throat, fever of 101 degrees, malaise, generalized aches and pains, pain beneath the xyphoid, and a slight cough. Acetylsalicylic acid and bed rest were prescribed. A few days later he noted bloody rhinorrhea. A lesion similar to the one on the arm appeared on the back. Local treatment to the nose and antibiotics afforded no improvement. "Spots" appeared on the posterior nasopharynx. Because of persistent malaise

Fig. 1.—Case No. 1. Chest x-ray made on admission, showing large mass lesion in right hilum.

and fever, he was referred to the Hospital of the University of Pennsylvania for diagnosis.

There was no allergic history, no history of renal disease, and the review of the systems was essentially negative. His mother had a successfully treated breast cancer.

On physical examination, he was weak, appeared chronically ill, and had a syncopal attack while the initial history was being recorded. Blood pressure was 140/80. Two punched-out, sharply demarcated ulcers were noted on the left arm, with very little surrounding inflammatory reaction. These were one centimeter in diameter and three to four centimeters deep. A similar lesion was seen over the left scapula. Bilateral perforations of tympanic membranes were found. An ulcer was seen on the left side of the nasal septum. The lungs were normal, and the heart showed a split first sound at the apex with an inconstant gallop rhythm. The rest of the examination was negative.

Initial laboratory study revealed a normal blood count, three to five per cent eosinophilia, blood urea nitrogen of fourteen milligrams per cent. The urine persistently showed albuminuria, hematuria, and hyaline casts. Serologic tests for syphilis were negative. Sinus x-rays showed mucous membrane thickening in all paranasal sinuses, and the mastoid films revealed evidence compatible with chronic otitis media. A chest x-ray showed a rounded mass lesion in the right hilum (Fig. 1). Tomograms did not show any calcium in this lesion. An intravenous urogram was normal. Skull x-ray was negative. Encephalogram was normal.

A bronchoscopic examination was made on March 14, 1958; this showed friable mucosa of the right main stem bronchus just below the right upper lobe opening. This was biopsied and reported to show a questionable epithelioma of the bronchus. The Papanicaloau stain was reported as showing evidence of a malignant process, but subsequent events showed this to be in error.

The skin lesion was biopsied, and a diagnosis of histoplasmosis was made on the basis of the finding of certain intracellular encapsulated organisms, but subsequent biopsies did not confirm the initial impression. A second bronchoscopic study was done on March 25, 1958, and tissue removed at this time was reported as squamous metaplasia of the right main bronchus.
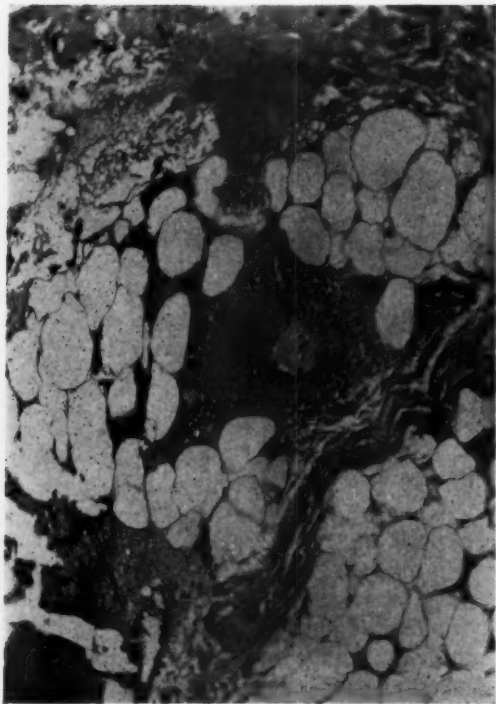
Fig. 2.—Case No. 4. Skin biopsy showing perivascular infiltration.

The patient became progressively sicker. He became weak and pale. The distal pulp of several fingers became very cyanotic, swollen, and resembled incipient gangrene. Nausea and vomiting appeared. By March 24, two weeks after admission, the blood urea nitrogen had risen to 64 milligrams per cent. He developed massive albuminuria. The hemoglobin fell slowly to 10.0 grams. Laboratory study confirmed the abnormal chemical picture of acidosis and uremia. A trial of steroid therapy was instituted, but no beneficial effect was produced. A deep necrotic and suppurative ulcer developed on the uvula and soft palate, making swallowing very painful and almost impossible. The course was rapidly downhill, with increasing uremia
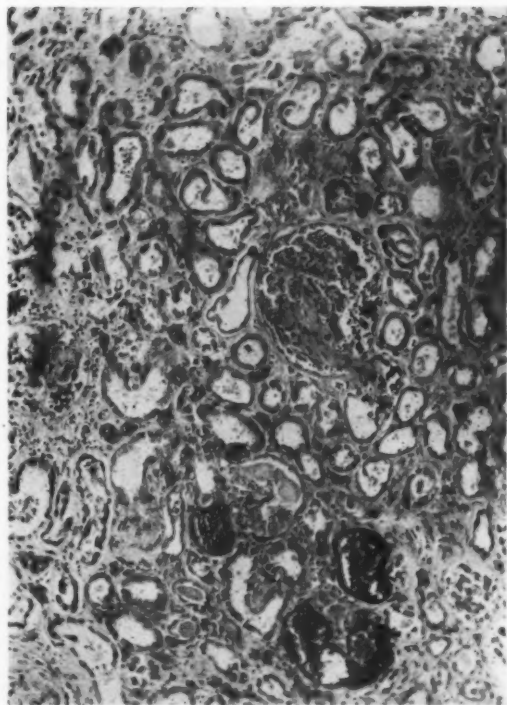
Fig. 3.—Case No. 1. Photomicrograph of kidney, showing glomerulitis and necrotizing vasculitis.

and a terminal blood urea nitrogen of 212 milligrams per cent. Death occurred on April 10, 1958, one month after admission and four months after onset of symptoms.

Necropsy findings included severe glomerulitis with uremia, necrotizing vasculitis of kidneys, lungs (necrotizing granuloma), adrenals, skin, nasal mucosa, and perforation of the nasal septum (Figs. 2, 3, 4).

Comment. This patient presents a typical picture of Wegener's granulomatosis. He developed a severe necrotizing granuloma of the nasal septum, ulceration and necrosis of the soft palate, and demon-
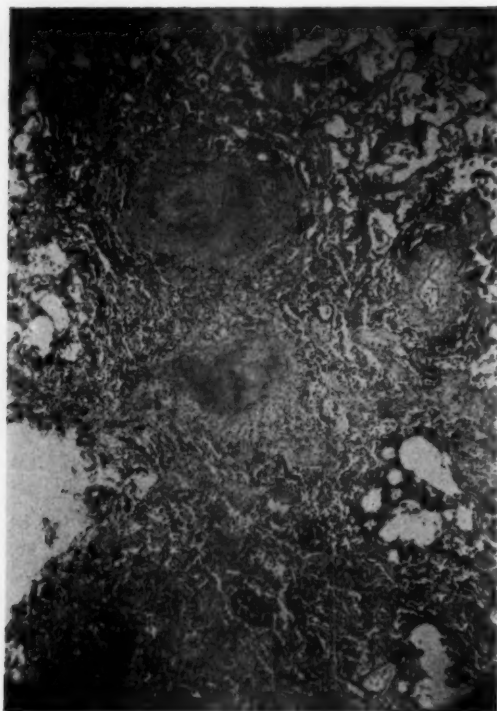
Fig. 4.—Case No. 1. Photomicrograph of right hilar lesion, showing severe vasculitis and necrotizing granuloma.

strated a hilar lesion that gave all the clinical appearance of a broncho-genic carcinoma. If his general condition had not deteriorated so rapidly, thoracotomy would have been seriously considered. The skin lesions were evidence of the diffuse vasculitis and characteristically he succumbed to renal failure ending in severe uremia. At no time did he present any significant joint phenomena or hypertension, and only slight eosinophilia was present.

CASE 2. J. P., aged 18 years, white male. The first admission to the Hospital of the University of Pennsylvania was on November 10, 1954 because of loss of voice and hoarseness. Onset of symptoms

Fig. 5.—Case No. 2. Lateral film of the neck, demonstrating involvement of the upper trachea and subglottic larynx.

was in March, 1953, and after local and antibiotic therapy for several months, he was bronchoscoped in January, 1954, and told that he had polyps and infection in the larynx. Patient developed dyspnea on exertion and cough, and he was bronchoscoped on several occasions for removal of granulomatous tissue. He was referred to the Hospital of the University of Pennsylvania for further study. During November, 1954, four biopsies of the vocal cords and subglottic area were done, which showed only "granuloma." The subglottic area was narrowed, and the tracheal lumen was reduced to four millimeters. The softness of the constriction suggested a cartilaginous defect in the upper larynx (Fig. 5).

During this hospitalization, a saddle nose deformity was noted, but after appropriate x-ray and serologic study, it was decided that congenital lues was eliminated; and no destruction of bone or cartilage of the nose was demonstrated. The impression was that this was a congenital lesion of no clinical importance. A blood count was normal. The urine showed one plus albuminuria, one to two erythrocytes per high power field, and one to two granular and hyaline casts per high power field. Kolmer and Kline tests were negative.

The second admission (July 26, 1955) occurred because he developed marked weakness, exertional dyspnea, and pallor. Physical examination showed pallor and saddle nose, but no other significant findings. Blood pressure was normal. Admission hemoglobin was 5.3 grams with normal white count. Blood urea nitrogen on admission was 22 milligrams and later rose to 26 milligrams. Serum creatinine was 2.0 milligrams. Urine on repeated examination showed albuminuria, red cells, and finely granular and hyaline casts. Bone marrow was hypoplastic. Study of the blood for lupus erythematosis cells was negative. Pulmonary nodulation was noted on x-ray of the chest and sinus x-ray revealed extensive mucous membrane thickening and some thinning of the bony walls of the sinuses.

Treatment consisted of blood transfusions and cortisone. The patient showed temporary improvement, and then died suddenly at home about four months later, presumably of suffocation, probably the result of acute airway obstruction. No necropsy was performed.

Comment. The destructive granulomatosis of the larynx, the pulmonary x-ray findings, and the evidence of renal insufficiency make the diagnosis of Wegener's granulomatosis quite likely.

CASE 3. J.M., aged 47 years, colored male. The patient was admitted to another hospital on February 19, 1958, because of swelling of face, hands, abdomen, and neck of three weeks' duration. Previously he had been well. Over the three week period, dyspnea appeared with increasing severity, so that he could not lie in bed without severe dyspnea and cough.

Previous medical history: he was treated for sinusitis in 1950; at that time the blood count and urinalysis were normal.

On admission, he was acutely ill and dyspneic. Blood pressure was 170/100. Respirations were 32 per minute. Temperature was

100 degrees orally. There was generalized edema, including edema of the abdominal wall and scrotum. He had a presystolic apical gallop rhythm and evidence of a right pleural effusion. Marked increase in venous pressure was noted.

Laboratory studies revealed a hemoglobin of 8.6 grams; 17,450 leukocytes with 85 per cent polymorphonuclears; four plus albuminuria; eight to ten erythrocytes per high power field, and granular casts. Blood urea nitrogen on admission was 114 milligrams.

Treatment consisted of oxygen, digitalization, salt restriction, and protein restriction. The patient improved considerably, and lost much of his edema. On March 5, his urine output fell to 500 cubic centimeters and increasing oliguria followed on successive days. Anemia persisted in spite of four transfusions. Blood urea nitrogen rose to 167 on March 10, and on March 12 the patient was transferred to the Hospital of the University of Pennsylvania for dialysis with the artificial kidney. Dialysis was performed on March 14 because of the oliguria, blood urea nitrogen of 168 milligrams per cent, and serum potassium of 7.5 milliequivalents. Prior to this procedure, it was determined that the bone marrow showed no evidence of multiple myeloma, and his clotting mechanism was grossly deranged. The type of abnormality was similar to that seen in uremia. The patient responded somewhat to the dialysis, and was then treated conservatively for the next 13 days. During this period, he received penicillin because of the finding of a beta hemolytic streptococcus in the throat culture, and prednisone, 20 milligrams four times daily. By March 27, he became nauseated, vomited, and developed intractable hiccups. On March 28, another hemodialysis was performed. Improvement in the chemical picture ensued, but a few days later tarry stools appeared. On April 3, 1958, he developed overwhelming pulmonary edema, had a generalized convulsion, and died.

This patient did not at any time show x-ray evidence of a lesion in the lung fields save for pleural effusion. Evidence of recurrent sinusitis was noted, however, by clinical and x-ray examination.

Necropsy examination revealed necrotizing vasculitis involving kidneys, lungs, adrenals, prostate, and liver. Generalized glomerulitis was noted.
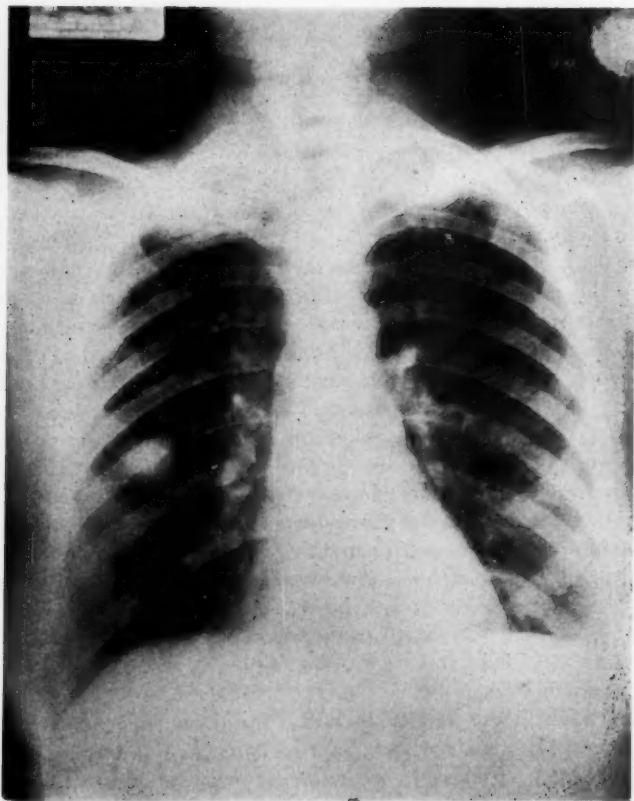
Fig. 6.—Case No. 4.   Chest x-ray made on admission.   The bilateral apical infiltration and the nodular lesion in the right mid lung field may be considered a variant of the usual appearance of the roentgenograms of the chest in Wegener's granulomatosis.

Comment. The pathologic evidence in this case is compatible with Wegener's granulomatosis, though the characteristic lung lesion is missing. The diagnosis of acute glomerulonephritis was entertained, but the generalized nature of the vasculitis was not in keeping with this diagnosis. Death was due to renal failure leading to uremia and pulmonary edema.

CASE 4. A.C., aged 45 years, white female. This 45 year old white salesgirl was admitted to the Hospital of the University of Pennsylvania on December 30, 1958, because of pain and swelling of the feet and arms. Present illness began in October, 1958, with bilateral earache and otorrhea. This was followed by congested eyes and rhinorrhea with swelling of the nose. In November, a sore swollen right ankle appeared, and migratory pains in shoulders, hips, wrists, and knees followed. In December, she developed low grade fever, night sweats, and cough. She was admitted to another hospital in this city, at which time bilateral apical infiltrative lesions were noted by chest x-ray, but subsequent study for tuberculosis proved to be negative. Eosinophilia of 15 to 20 per cent was found. Hematuria, increased serum globulin, and elevated sedimentation rate were also discovered. Butazolidin was prescribed and the patient was discharged. Two days later, she developed a diffuse petechial rash. There was a past history of positive skin tests to house dust and feathers.

On physical examination at the Hospital of the University of Pennsylvania on December 30, 1958, the patient showed pallor, a diffuse hemorrhagic skin rash, acute conjunctivitis, bilateral iridocyclitis, ulceration of the nasal septum, scattered coarse rhonchi, decreased breath sounds over the right apex, symmetrical swelling of the ankles, knees, and right second and third metacarpophalangeal joints.

A chest x-ray showed clouding of both apices, and a nodular infiltrate in the right mid lung (Fig. 6). Sputum and gastric washings were negative for tubercle bacilli. Tuberculin skin test was negative. Skin biopsy showed a necrotizing arteritis with ulceration. The urine showed albuminuria, cylinduria, and hematuria. The admission blood urea nitrogen was 22 milligrams per cent.

The patient's course was rapidly downhill with increasing oliguria, rising blood urea nitrogen to a final level of 188 milligrams

per cent, spreading skin hemorrhages with central areas of necrosis and increasing uremia. In spite of antibiotics, steroids, blood transfusions, and adequate electrolyte replacement, the patient died on January 14, 1959, two weeks after admission and about three months after the onset of present illness.

At necrospy, the findings included bilateral apical granulomata with cavitation, a granuloma in the right middle lobe, petechia on the surface of the kidneys. Histologic study demonstrated a generalized necrotizing arteritis, focal necrotizing granulomata of lungs, liver, adrenals, and spleen, fibrinous pericarditis, and terminal pneumonia.

Comment. The nodular lesion in the right mid-lung was at first considered to be a metastatic lesion, but the subsequent course and findings confirm the impression of Wegener's granulomatosis. At this hospital this patient presented eosinophilia of 16 per cent, and in addition showed more arthritic phenomena than usually seen in this syndrome; thus, she presents more of the picture of polyarteritis nodosa than the other patients, but by no means fails to satisfy the criteria of Wegener's granulomatosis.

REPORT OF CASES OF NON-FATAL GRANULOMAS
OF THE RESPIRATORY TRACT

CASE 5. J.G.McM., aged 54 years, white male. This patient was admitted to the Hospital of the University of Pennsylvania on October 16, 1958. He gave a history of hoarseness of two years' duration. Hospitalization for further study was advised two years ago, but the patient refused. For three months prior to admission, he noted increasing exertional dyspnea, loss of ten pounds in weight, and some difficulty in swallowing, increasing cough productive of thick, white sputum and increasing hoarseness. On October 14, 1958, at another hospital, direct laryngoscopy was done. The larynx was found to be almost completely occluded, and an emergency tracheotomy was done on that date. Transfer to the Hospital of the University of Pennsylvania was made on October 16, 1958, with a tracheotomy tube in place. He was admitted with a low grade fever.

Repeated examinations at this hospital showed only granuloma in the subglottic area, with extension in the trachea almost to the

bifurcation. This latter involvement subsequently cleared prior to discharge. A staphylococcus, coagulase positive, was cultured from the tracheostomy, and the patient was treated with appropriate antibiotics.

Studies done during his hospitalization showed no evidence of any renal abnormality or renal functional impairment. Search for lupus erythematosis cells was negative. Serum albumin and globulin were normal. Repeated urinalyses were negative, and hematologic status was normal. A chest x-ray and sinus x-rays were negative. A urogram was normal.

Biopsies of the tracheal granuloma yielded only granuloma as a diagnosis. No evidence of vasculitis was found. Cultures of this material were negative for tuberculosis or mycoses.

Comment. At the time of this report (March, 1959), the patient remains in good general health. He is being carefully observed for the possible development of skin lesions, ensuing renal insufficiency, or evidence of a pulmonary neoplasm. A consideration of x-ray therapy to the subglottic area and trachea is being entertained; but thus far, the subglottic area appears to be clearing, though there is still impaired motility of one cord.

CASE 6. S.L., aged 42 years, white female. This patient was first admitted to the Hospital of the University of Pennsylvania on April 13, 1952, at age 35 with a three year history of dyspnea and wheezing on exertion. These symptoms became progressively more severe, and very slight exertion would be followed by severe dyspnea and paroxysms of cough. A bronchoscopic examination done at another hospital showed a "growth" in the trachea, and she was transferred to the Hospital of the University of Pennsylvania. Systemic review, past medical history, and family history were non-contributory.

Physical examination showed a thin, chronically ill, white woman with blood pressure of 100/66. Except for expiratory stridor and wheeze, the examination was negative. There was no lymphadenopathy or splenomegaly.

Fig. 7.—Case No. 6. Photomicrograph of bronchial biopsy made in April, 1952, showing nonspecific granuloma.

Bronchoscopy on April 15, 1952, showed that the distal end of the trachea was narrowed, and both main bronchi were definitely narrowed in caliber. The area was biopsied, and reported as showing a granuloma of the bronchus (Fig. 7). A tuberculin skin test was negative. Blood counts, urinalysis and blood chemistry, including determinations of serum albumin and globulin, were all normal. The patient was again bronchoscoped on April 22, and biopsy material was again reported as showing granuloma. No evidence of lymphoma was found. The patient became very dyspneic, and intravenous ACTH was administered for several days by continuous infusion. The pa-

tient showed dramatic improvement, and on April 28, 1952, a lymph node was removed from the left axilla. This node was diagnosed as reticulum cell hyperplasia. X-ray therapy was begun to the anterior mediastinum on May 1, 1952, and continued for two weeks. At the time of discharge on May 23, she was much improved symptomatically, and showed much improved aeration of the lung fields. No definite diagnosis other than granuloma was ever established at that time. A final bronchoscopic examination on May 19 showed a considerable improvement in the endotracheal and endobronchial picture.

The patient was admitted a second time on January 23, 1956, reporting that she had been bronchoscoped elsewhere several times in the intervening years, and that further x-ray therapy had been given to the anterior mediastinum. She was also given steroid therapy intermittently. She was admitted at this time because of suggested superior vena cava obstruction, resulting in slight edema of the face and neck. A few small shotty nodes were found in the left supraclavicular areas; biopsy showed chronic lymphadenitis. Bronchoscopy on January 24, 1956, showed stenosis and fixation of the tracheal bifurcation. Blood and hematologic study remained normal. One urinalysis showed a trace of albumin. She was discharged on February 5, 1956.

The third admission was on June 13, 1957, and resulted from increasing exertional dyspnea and cough. Physical examination was unchanged, and no new findings were elicited or discovered after a repeat bronchoscopy and laboratory investigation. She was discharged on June 19, 1957.

The patient was re-admitted on November 13, 1958, because her previous symptoms had exacerbated and re-study was indicated. At this time, the veins of the anterior chest wall, abdomen, and about the umbilicus were quite prominent and distended. The patient was again studied intensively. A bronchoscopic examination on November 21, 1958, revealed cicatricial stenosis of both main bronchi. No tissue was available for biopsy. Complete renal function study was negative. A venogram showed occlusion of the right subclavian vein, and showed that the veins of the upper body apparently emptied into the inferior vena cava. Liver function was found to be normal. The patient was discharged on November 27, 1958, on broncho-dilators

Fig. 8.—Case No. 7.   Lateral roentgenogram of neck showing the non-specific granuloma intruding on the air column of the trachea.   The naso-esophageal tube indicates the relation of the esophagus to the lesion.

and inhalant therapy with no etiologic diagnosis.   Attempts to make a diagnosis of histoplasmosis failed, though she had a positive histo-plasmin skin test on this admission.

The patient was seen on a follow-up visit on January 27, 1959. Her symptoms and physical examination were unchanged.   Decadron was started at this time and subsequent follow-up visits are to be made.

Comment.   This patient has a nine year history of a granuloma-tous process in the trachea and main bronchi with no systemic involve-

ment. There has been no etiologic agent discovered, though lymphoma, histoplasmosis and Wegener's granulomatosis have been suggested. X-ray therapy and steroid therapy presumably played a dramatic role in the relief of severe obstructive symptoms in 1952, and have possibly helped control her disease subsequently. Complete diagnosis must await further development.

CASE 7. W.L., aged 54 years, white male. The patient was admitted on May 2, 1949, because of hoarseness and wheezing of six months' duration, beginning after a "heavy cold" in October, 1948. Previous history was negative except for a cholecystectomy in 1946 for calculous cholecystitis. Physical examination was negative.

Laryngoscopy showed an ulcerated, fungating and obstructive lesion below the cords. Pathologic report on repeated specimens was lymphoid tissue or granulation tissue. Blood count and urinalysis were normal.

The patient has been followed at intervals since 1949, and subsequent direct laryngoscopic examinations have shown persistence of a granulomatous process. An x-ray examination on March 8, 1951, continued to show considerable swelling in the region of the larynx. The trachea was displaced anteriorly and encroached upon (Fig. 8).

Re-admission on June 10, 1954, was necessitated because of severe hoarseness of three weeks' duration, but otherwise he was in good health. The general physical examination was not remarkable. A blood count and urinalysis were normal. A chest x-ray was negative. Direct laryngoscopy showed inflammatory thickening of most of the posterior portion of the larynx. Biopsy was again reported as granuloma of the larynx. The patient had a low grade fever for a few days, but was discharged on June 16, 1954, as improved.

At the time of his last examination on August 31, 1954, the larynx was much improved. There was only minimal residual swelling, and a small whitish area just anterior to the vocal process of the left cord.

Comment. Over a five year period, this patient was observed with a localized granulomatous process of the larynx. No systemic effect has been discovered. No chest lesion has developed, and at the time of this report the patient remains in good health. A diagnosis

of Wegener's granulomatosis seems unlikely at this time, unless mild or slowly developing variations of this clinical syndrome exist or become apparent with further observation.

<div align="center">COMMENT</div>

All of these patients have in common a granulomatous lesion of the respiratory tract. In Case 2, the lesion of the lung was considered initially to be a bronchogenic carcinoma. This is not unusual. Other cases reported in the literature have been similarly diagnosed. The lungs are so frequently involved in this disease that a pulmonary shadow can lead most easily to a presumptive diagnosis of lung cancer. The positive cytologic report in our case was most disconcerting, because false positive diagnoses of bronchogenic cancer are extremely rare in our clinic. The group of four patients presented first showed definite evidence of glomerulitis with albuminuria, hematuria, casts, and ultimate renal failure; though in Case 2, respiratory obstruction must be presumed to be the immediate cause of death. Although it was reported to us that he died in respiratory distress, there was no significant respiratory obstruction at the time we last saw him alive.

The second group of three cases do not conform to the criteria now required for a diagnosis of Wegener's granulomatosis, but they do present granulomatous lesions of the airway, all of which have been sufficiently serious to threaten life to a very serious degree. It seems impossible to believe that Case 6 could have survived without the dramatic reprieve which followed the institution of steroid and x-ray therapy. At the time such a patient is first seen, it is desirable to determine whether or not this particular granuloma has the potentialities of Wegener's granulomatosis, or if its potentialities are less ominous. Unfortunately, the pathologist cannot make a definitive diagnosis of Wegener's granulomatosis from biopsy material obtained from the sinuses, larynx, or trachea. The moisture, the ulceration, and secondary bacterial invasion cloud the picture. Frequently, all he can report is a granulomatous lesion, and the evidence of vasculitis may not be recognizable because it cannot be differentiated from the effects of secondary infection. In these same cases, post mortem findings may show the characteristic evidence of active or healed pulmonary vasculitis. In the evaluation of a patient such as this, one must be alert to the diagnosis on clinical grounds, because a pathognomonic biopsy specimen may not be obtainable. It seems significant that several

observers[13,21] call attention to the fact that the lesions, wherever they are found, appear to be in different stages. It seems reasonable to assume that there are recurring episodes of angiitis, and this probably is not necessarily a continuous process. It is possible, therefore, that this disease is the effect of a series of insults by some noxious agent; and if the effects of these insults can be reduced, the disease may be ameliorated. There appears to be a strong feeling among those who are familiar with this disease that steroid therapy possibly combined with x-ray therapy can delay the disease process, but it is certain that there is a point where the degree of renal damage makes recovery impossible. The early recognition and identification of the process would, therefore, seem to offer therapeutic possibilities.

Walton[12] has suggested that the respiratory lesions are the primary lesions. The wide spread lesions occur later in the natural history of the disease. These secondary lesions may be due to a hypersensitivity reaction stimulated by drug or tissue breakdown products. Such a concept makes necessary careful study of the whole patient when a granuloma of the upper or lower respiratory tract is discovered. It goes without saying that intense concern must be exhibited for the local lesion. Endoscopic study, biopsy, bacteriologic study, and so forth are as important as ever. But it is apparent that the evaluation of the patient will be impossible unless a broad view of the problem is held. We feel sure that when the medical profession becomes more aware of Wegener's granulomatosis, a far larger number of cases will be recognized. By achieving a diagnosis at the earliest possible stage, greater therapeutic opportunity exists for the patient, and a greater opportunity for an increase in our knowledge of this disease will be achieved.

SUMMARY

Four cases of Wegener's granulomatosis are described and the literature reviewed. Wegener's granulomatosis is a syndrome consisting of necrotizing granulomata of the upper and lower respiratory tract, generalized necrotizing vasculitis, and glomerulitis leading to uremia and death.

Three patients with serious granulomata of the respiratory tract are described with the thought that these may represent early or non-fatal variants of the syndrome.

The otolaryngologist should be cognizant of this disease because of the frequency with which its initial manifestations involve the respiratory tract.

3400 SPRUCE ST.

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Scientific Papers of the American Broncho-Esophagological Association

XXXIX

BRONCHOLITHIASIS

HERMAN J. MOERSCH, M.D.

HERBERT W. SCHMIDT, M.D.

ROCHESTER, MINN.

Broncholithiasis, or bronchial stone, is one of the most interesting of pulmonary diseases. Although it was first described more than 350 years ago, it received scant attention until recent years. As late as 1944, Tinney and Moersch[1] were able to find reports of only 30 cases of broncholithiasis or so-called lung stone in the British and American literature. They made a report of 28 additional cases collected from the records of the Mayo Clinic. This scarcity of cases reported in the literature in no way represents a true index of the frequency with which broncholithiasis occurs. Unfortunately, in the past there has been failure to appreciate the fact that broncholiths possess the ability to mimic a great variety of pulmonary diseases and that they masquerade under false colors. Consequently, they have gone unrecognized. The expectoration of calcareous material, which is so diagnostic of broncholithiasis, is often forgotten by the patient, and such a history is missed unless specifically sought after. The increasing frequency with which exploratory thoracotomy is performed today for indeterminate pulmonary lesions has substantiated the impression that broncholithiasis is not an uncommon pulmonary finding. Schmidt and associates[2] were able to collect 13 cases of broncholithiasis encountered at the clinic between 1944 and 1949, and since then we have collected 58 additional cases up to January, 1959.

Broncholiths originate primarily from three sources. They may develop within the lumen of the bronchus subsequent to the deposit of calcium about a foreign-body nucleus. They may occur as a consequence of calcification or ossification of the elastic cartilage of the bronchus with subsequent sequestration of the calcified material into the bronchial lumen. Most broncholiths, however, occur as the result of erosion and protrusion of calcified hilar and paratracheal nodes into the tracheobronchial tree. The etiology of calcification of the hilar and paratracheal lymph nodes is varied and often unknown. It is generally assumed that tuberculosis is the primary cause for such calcification, an assumption that often lacks confirmation. In only three of the 99 cases in the present study could tuberculosis be proved. Tuberculin skin reactions in a third of the patients with broncholithiasis will be found to be negative. It is possible that in certain instances calcification of hilar and paratracheal lymph nodes is due to granulomatous diseases such as histoplasmosis and coccidioidomycosis.

Broncholiths vary considerably in size and consistency. They are usually irregular in shape, have pitted surfaces, and are grayish white (Fig. 1). They may be single or multiple. In one case a patient was reported to have expectorated more than 400 broncholiths. Most broncholiths are hard and gritty, but on occasion they may be somewhat puttylike in consistency.

DATA ON 99 PATIENTS WITH BRONCHOLITHIASIS

Up to January 1959, 99 cases of broncholithiasis have been encountered at the clinic. Only those cases are included in this study in which the patient presented a clear-cut history of having expectorated one or more broncholiths, in which a bronchial stone was found free in the tracheobronchial tree and was removed bronchoscopically, or in which a broncholith was found free in a bronchus in a surgically resected lung. No cases were included in which calcified nodes were demonstrable on roentgen examination of the thorax or in which bronchoscopy showed pressure on a bronchus, although the gland had not completely eroded into the bronchial lumen. In our experience, a broncholith was demonstrated in only one of every ten cases in which it was suspected.

The youngest patient in our study was 22 years of age and the oldest was 81. The majority of patients were between 40 and 60 years of age. The cases were almost equally divided as to sex, 49 patients being men and 50 women. The patients came from 25

Fig. 1.—Broncholith in bronchus.

different states in the United States, the greatest number coming
from Iowa, Illinois and Indiana.   It was of interest that none of the
patients resided in Minnesota.

Symptoms.   The symptoms associated with broncholithiasis de-
pend on the size of the broncholith, its location in the tracheobron-
chial tree, and the degree of bronchial obstruction it produces.   A
small broncholith that does not obstruct the bronchus, like a small
nonobstructive, aspirated foreign body, may reside in the bronchial
tree for years without producing symptoms.   Five of the patients in
the present study had broncholiths of this type.   The great majority
of broncholiths do produce bronchial obstruction to some degree
and consequently cause pulmonary symptoms.   The duration of
symptoms in our study was found to vary considerably.   In three
cases the symptoms were of less than 1 month's duration, while in six
others pulmonary symptoms had been present for more than 20
years.   In the majority of cases the symptoms were of less than 2
years' duration.

The erosion of a calcified node into the lumen of the respiratory
tree may occur without producing immediate symptoms.   In con-
trast, it may be a dramatic event heralded by a severe paroxysm

of coughing, associated with wheeze, dyspnea, bleeding, thoracic pain and a sense of strangulation.

Cough is by far the commonest and the earliest symptom associated with broncholithiasis and was present in 80 per cent of our patients. The cough at first is usually dry and nonproductive, only to be productive eventually of mucoid, then mucopurulent secretion after episodes of acute respiratory infection. The cough may be intermittent or constant in nature, depending on the presence of infection and the position of the stone in the bronchial tree.

Half of the patients with broncholithiasis experience bouts of chills and fever, which are provoked by obstruction of a bronchus by a broncholith and superimposed bronchial infection. These bouts of chills and fever are often looked on as bouts of pneumonia. The fever generally lasts three to seven days and subsides with the expectoration of purulent material which often has a pungent odor.

Hemoptysis was the second most frequent symptom, being present in two-thirds of our cases. On occasion it may be the first symtom. The amount of bleeding may vary considerably. Generally it is small, that is, less than half a cup in 24 hours; however, it tends to recur. On occasion it may be copious in amount, and sufficient to endanger the life of the patient; in such cases transfusions of blood are necessary.

Forty-four patients gave histories of expectorating one or more broncholiths. One patient stated that he had coughed up 103 stones. It is surprising how frequently patients who had coughed out stones completely forgot the incident and recalled it only after another stone had been found at bronchoscopy or operation.

In 25 per cent of our cases the patients complained of pain. It varied from the sharp, tearing variety associated with rupture of a calcified gland into the bronchial lumen, to an indefinite sense of discomfort confined to that portion of the thorax where the broncholith had produced a bronchial obstruction. Large broncholiths located in a large stem bronchus or the lower portion of the trachea were found to produce wheeze, which was often incorrectly interpreted as asthma. The term, "stone asthma," has been applied to this condition. Broncholiths that are large enough to produce wheeze may also cause dyspnea.

The following case represents a rather characteristic clinical history of a patient with broncholithiasis:

Fig. 2.—Poorly defined mass in anterior-inferior region of the right upper lobe with marked calcification of the hilar nodes. *a*. Posterior-anterior view. *b*. Lateral view.

CASE 1. A 68-year-old man had been well until two years before coming under our observation. At that time a cough suddenly developed and was persistent in nature. A week or so later, it was accompanied by fever associated with chills. A diagnosis of pneumonia was made by his attending physician. He was given penicillin with prompt subsidence of the fever and chills but with no appreciable effect on the cough. The subsidence of his fever and chills was associated with the expectoration of a small amount of foul-smelling sputum. During the next two years, he had ten similar episodes of chills and fever, all of which were diagnosed as pneumonia; each time he responded to penicillin therapy. A week before he came to the clinic, he expectorated blood for the first time. A roentgenogram of the thorax revealed a poorly defined mass in the anterior-inferior region of the right upper lobe with marked calcification of the hilar nodes (Fig. 2*a* and *b*). The results of all routine laboratory studies, which included cytologic examination of the sputum for carcinoma cells and bronchial smears for tuberculosis, were negative. Bronchoscopic examination revealed a broncholith obstructing the anterior segment of the right upper lobe; it was removed with prompt relief of symptoms.

Physical Findings. Physical findings vary considerably in patients with broncholithiasis. Small broncholiths do not tend to cause
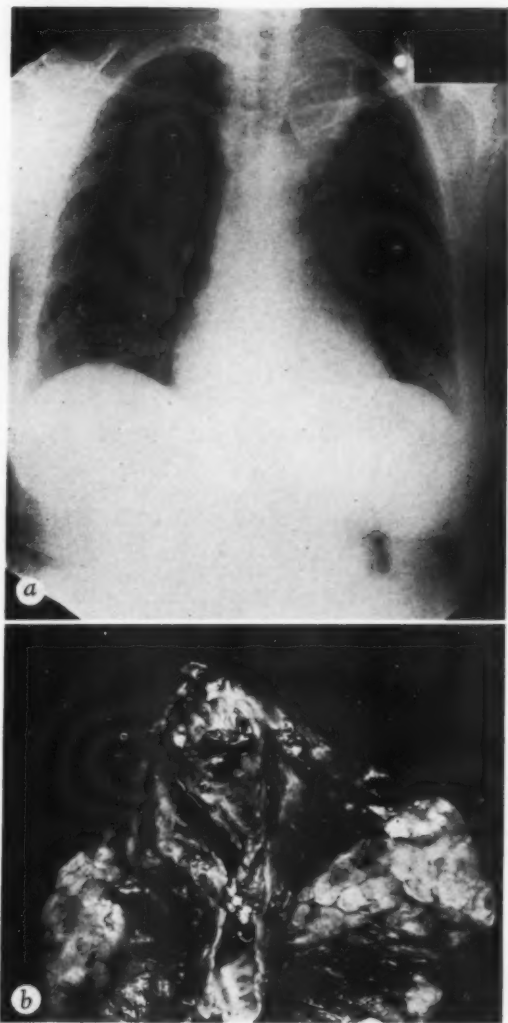
Fig. 3a.—Roentgenogram showing an area of collapsed lung with area of calcification at apex of contraction.   b. Gross appearance of lesion in re-sected specimen with presence of broncholiths.

Fig. 4.—Case of broncholithiasis with pulmonary lesion present but no calcification apparent.

altered physical findings. The changes that do occur depend in large measure on the size of the broncholiths, their number and location, and the degree of bronchial obstruction they produce, along with the presence or absence of secondary bronchopulmonary infection. At best, physical examination is seldom diagnostic of broncholithiasis.

Roentgenologic Findings. Roentgenograms of the thorax may be of great value in the diagnosis of broncholithiasis and may furnish the first clue to the correct diagnosis. The most striking diagnostic roentgenologic feature is the presence of a calcified mass in a bronchus or the presence of a partially collapsed lung with dense calcification at its apex (Fig. 3*a* and *b*).

Experience has made the roentgenologist increasingly aware of the possibility of broncholithiasis whenever calcified glands are seen in association with pulmonary pathologic changes. In the first 41 cases

included in this study, which were reported by Schmidt and associates[2] in 1950, the roentgenologist suspected broncholithiasis in only three instances. In the 58 cases encountered since then the roentgenologist suspected broncholithiasis ten times; in seven other cases attention was called to the presence of calcified hilar and paratracheal glands, and in 11 others pulmonary lesions were described which contained areas of calcification. In 24 of the last 58 patients a pulmonary lesion was described (Fig. 4) but no calcification was noted, and in only six cases the roentgenograms of the thorax did not show evidence of abnormality. The pulmonary lesions with which broncholithiasis is most frequently confused roentgenographically were pneumonia, bronchiectasis, bronchogenic carcinoma and tuberculosis.

Unless one is aware of the significance of calcification in a roentgenogram of the thorax, it is startling how large a broncholith may be completely overlooked. The following case is an example:

CASE 2. A 54-year-old man had enjoyed good health until three years prior to his admission to the clinic. At that time a persistent cough had developed which at first was nonproductive but gradually became productive of small amounts of purulent sputum. At times the sputum was blood-streaked. Some time later he became aware of gradually increasing dyspnea brought on by exertion. A diagnosis of bronchiectasis had been made by his home physician and he had been treated with injections of penicillin and streptomycin with little benefit.

At the time of our examination it was noted that the patient had an audible wheeze brought on by exertion or a bout of coughing. The roentgenogram of the thorax was reported by the radiologist to be without evidence of a pathologic condition although a large deposit of calcareous material was present along the right side of the mediastinum in the hilar region (Fig. 5). On bronchoscopic examination, a large broncholith was found which obstructed the right main-stem bronchus. The broncholith appeared to project into the lumen of the bronchus from an opening in the medial wall of the bronchus. While the broncholith was being manipulated preparatory to extraction, considerable bleeding occurred. The broncholith was of such size that it was impossible to extract it through an 8.5-mm Negus bronchoscope, and it had to be removed along with the bronchoscope. After removal of the stone it was found to measure 1.5 cm in diameter. It was appreciated that undoubtedly more calcareous material remained in the bronchus but because of the bleeding it seemed advisable at the time to postpone further examination until the bleeding
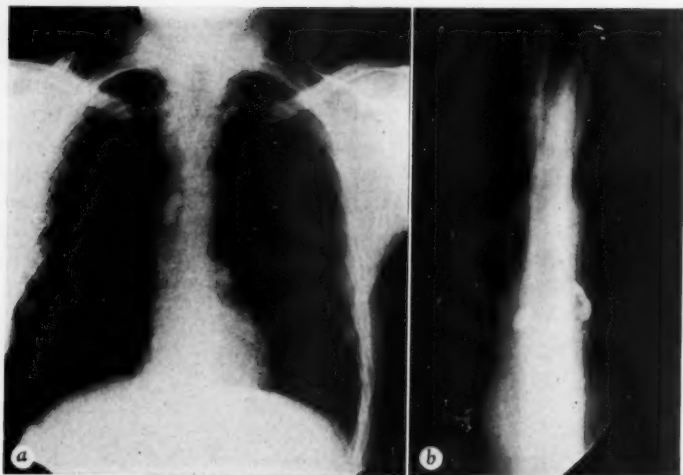
Fig. 5a.—Roentgenogram shows evidence of a large area of calcification along the right side of mediastinum in hilar area. b. Tomogram showing areas of calcification in course of both the left and right stem bronchi.

had subsided. Five hours later, to our great concern marked respiratory distress suddenly developed with expiratory and inspiratory stridor, rapidly developing cyanosis, and evidence of impending shock. We feared that another broncholith had become lodged in the trachea and immediately performed a second bronchoscopy. As anticipated, another large broncholith was found resting on the corina, almost completely obstructing the airway. The stone again was too large to be brought out through the bronchoscope and had to be removed along with the scope. It, too, measured 1.5 cm in diameter.

The patient's breathing immediately improved but the next day he again began to have increasing difficulty with respiration with a return of his wheeze. At this time a decrease in the breath sounds was noted over the left side of the thorax. A tomogram revealed a calcified mass obstructing the left and right main stem bronchi (Fig. 5b). On bronchoscopy a mass of granulation tissue was found projecting into the right main-stem bronchus from the medial wall, undoubtedly the site where the calcified material had eroded into the bronchus. Most of the granulation tissue was removed easily with forceps. On introducing the bronchoscope into the left bronchus, two large broncholiths were encountered which almost completely

obstructed the lumen. They also were too large to be withdrawn through the bronchoscope and had to be removed along with the instrument. Each measured 1.4 cm in its greatest width. After their removal, two smaller bronchial stones were removed from the left lower-lobe bronchus. The patient was completely relieved of his pulmonary symptoms and the calcified mass originally seen on the roentgenogram was no longer discernible. The broncholiths removed from this patient comprised the largest amount of calcareous material removed from any one patient in our series.

Bacteriologic Studies. Examination of the sputum of the patients in the present study was surprisingly noninformative. The sputum was studied by direct smear or culture for tuberculosis in 84 of the 99 cases. In only one case was the sputum found to be positive for Mycobacterium tuberculosis. Segmental resection of the lung was performed on this patient. A broncholith was found in a bronchus, and cultures and guinea pigs inoculated with resected lung tissue showed positive results for tuberculosis. In a second case, direct smears of the sputum were negative for acid-fast organisms, but at operation active tuberculosis was found as well as a broncholith, and the diagnosis was confirmed by the positive reaction of guinea pigs to inoculation. In a third case, cultures of the bronchial secretions were negative for acid-fast organisms, but the cultures of the gastric washings proved positive for acid-fast organisms. This patient underwent resection of the upper left lobe, and the diagnoses of both broncholithiasis and tuberculosis were confirmed.

In no case in the present study did cultures of the broncholiths that were expectorated or removed endoscopically or surgically show Mycobacterium tuberculosis, histoplasmosis or any other fungous disease. Eleven patients seen since 1949 showed positive skin reactions to histoplasmin. Tuberculin skin tests showed negative results in 10 of 33 patients.

Bronchoscopy. Bronchoscopy was found to be of value not only in the diagnosis but also in the successful treatment of broncholithiasis. Eighty-seven of the 99 patients were examined bronchoscopically and 12 were not. The 12 patients who were not examined bronchoscopically had expectorated one or more broncholiths, and at the time of our examination they were no longer having pulmonary symptoms and the physical examination and roentgenographic examination of the thorax showed nothing abnormal. Broncholiths were found in 38 of the patients and were removed successfully in 33 instances. In four of the five instances in which removal of broncholiths could not be accomplished successfully at the time of bronchoscopy, the

Fig. 6.—Broncholith associated with carcinoma of the bronchus.

patients were operated on and the broncholiths were removed by pulmonary resection. In the remaining case surgical treatment was refused and the patient continued to have pulmonary symptoms. The expectoration of one or more broncholiths does not exclude the possibility of finding more stones on bronchoscopy. In approximately half of the patients who reported that they had coughed up broncholiths, stones were found on bronchoscopic examination. In 35 patients bronchoscopy failed to reveal a broncholith but showed evidence of other bronchial difficulty such as bronchial stricture, localized granulation tissue, deformity of the bronchus, or pus and blood exuding from a specific bronchus. In only 14 of the 87 patients who were examined bronchoscopically the results of the examination were entirely negative.

Broncholiths seen through the bronchoscope vary considerably in appearance. They may be completely free within the lumen of the

bronchus, with no or scant evidence of associated bronchial irritation. They may be small or large, single or multiple. More often than not, they are surrounded by and embedded in granulation tissue. In those instances in which there is a stricture of the bronchus associated with the broncholith, the stone occasionally may be glimpsed below the stricture. Even though a broncholith is seen and removed from a granulomatous or strictured area, it is always wise to remove secretion and tissue, when feasible, for microscopic examination, culture and cytologic study, for broncholiths may be associated with other types of serious pulmonary disease, as illustrated in the following case:

CASE 3. A 62-year-old man had enjoyed good health until two years before coming under our observation. At that time a persistent cough developed with expectoration of a brownish sputum. This continued until three months prior to the patient's admission, when he suddenly suffered a severe pulmonary hemorrhage. Since the hemorrhage he had been aware of a respiratory wheeze. At the time of our examination a roentgenogram of the thorax showed a small circumscribed lesion in the medial aspect of the right lower lobe (Fig. 6). Bronchoscopic examination revealed a broncholith in the right bronchus intermedius. There was considerable infiltration in the wall of the bronchus at the site of the bronchial stone. With the loosening of the broncholith there was considerable bleeding and the stone was coughed out through the bronchoscope. Bronchial smears were taken from the right bronchus intermedius and specimens for biopsy were removed from the area of infiltration. Both bronchial smears and biopsies showed positive evidence for squamous cell carcinoma. The patient was operated on and the diagnosis of carcinoma of the bronchus was confirmed.

Location of Broncholiths. Broncholiths, like aspirated foreign bodies, can be found anywhere in the tracheobronchial tree and can move from place to place. Most bronchial stones tend to remain localized to a rather restricted segment of the respiratory tree. Like aspirated foreign bodies, broncholiths are found more frequently on the right side than on the left. Records were available as to the exact location of the broncholith in 68 of the 99 patients in the present study. In 48 cases the broncholiths were on the right side, and in 20, on the left side. In one case, although the broncholith originally was located in the right main-stem bronchus, portions of it eventually were found in the trachea and the left bronchial tree. Calcified hilar and paratracheal nodes can be expelled from the body by routes other than the respiratory tree. They may be expelled by way of the
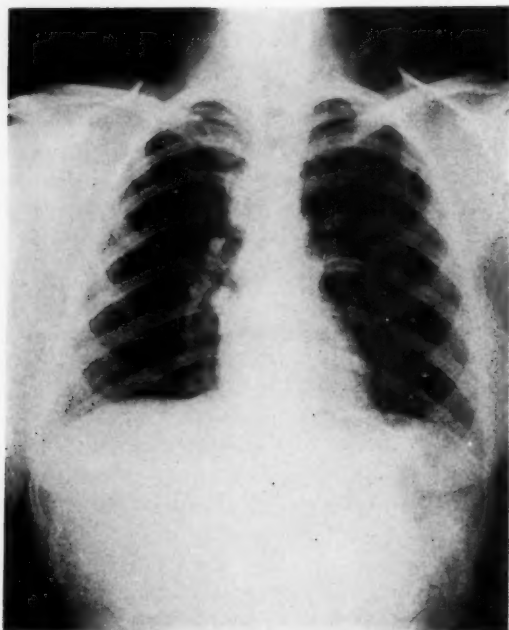
Fig. 7.—Evidence of a mass of calcified nodes is apparent in the right hilar and paratracheal regions.

esophagus or by external communication, as illustrated in the following case:

CASE 4. A 35-year-old woman had first noted a swelling over the suprasternal notch 10 years prior to coming to the clinic. This swelling was incised by her home physician and purulent material drained from it. The wound drained for three months and then healed. Nine years later, an abscess developed in the same area. This time the swelling was associated with chills and fever. She was given injections of penicillin with prompt subsidence of the fever and chills and disappearance of the abscess. Three months later the abscess again appeared in the same area but again disappeared with penicillin injections. It reappeared three months later, however, larger than ever. At this time the abscess was incised with drainage of purulent material, and several small calcified masses were extracted from the operative wound. Several days later the patient experienced a paroxysm

of severe coughing and expectorated several small broncholiths.   At
the time of our examination she was found to have a draining sinus
in the suprasternal notch.   A roentgenogram of the thorax showed
evidence of a mass of calcified nodes in the right hilar and para-
tracheal regions (Fig. 7).   Tuberculin skin tests gave negative results,
and material cultured from the wound in the suprasternal notch was
reported negative for tubercle bacilli.   Bronchoscopy revealed granu-
lation tissue on the right lateral wall of the lower end of the trachea
but no broncholith could be seen.   After this, the sinus in the supra-
sternal notch healed.   In this case, calcareous material had been ex-
pelled both by way of the tracheobronchial tree and by way of the
suprasternal notch.

Surgical Considerations.   Exploratory thoracotomy is of great
value in the diagnosis of broncholithiasis and is often the only method
by which an antemortem diagnosis can be established.   Combined
with pulmonary resection, it permits the removal of the calcareous
material along with the portion of the lung that may have been dam-
aged by its presence.   In the past ten years, from January 1949 to
January 1959, during which time 58 patients with broncholithiasis
were seen, the diagnosis was established in 21 instances by means of
exploratory thoracotomy.

Surgical treatment with resection of part or all of a lung was
done in 38 cases in the present study.   In all but four of the 38 cases
bronchial stones were found at the time of operation.   In one of the
four cases a broncholith had been found in association with a broncho-
genic carcinoma but it had been removed at the time of previous
bronchoscopy.   In the other three cases the bronchial stones had been
expectorated preceding operation but in each case a bronchial stricture
with bronchiectasis and pneumonitis was present.   In one additional
case operation had been performed elsewhere, and no record was
available as to whether or not a stone was found.

In the cases in which operation was performed, the broncholiths
were found to be on the right side in 29 cases and on the left side in
nine.

The results of operation in the treatment of broncholithiasis were
highly satisfactory in most cases.   Two of the 38 patients who under-
went operation died; one died six days after operation from a cerebral
infarct and another died at home of an unknown cause 19 days after
operation.   Pneumonitis and bronchiectasis invariably were found in
association with the broncholiths in the patients who were treated
surgically.

Treatment. If a patient expectorates a broncholith and subsequently does not suffer further pulmonary symptoms, and if the roentgenogram of the thorax does not show evidence of abnormality, no further treatment is necessary. Because broncholiths may have multiple sites of origin, it is advisable to be as conservative as possible in removing functioning pulmonary tissue. Whenever possible, bronchoscopic removal of broncholiths should first be attempted, but if this fails or if the question of diagnosis is not certain, exploratory thoracotomy with as conservative pulmonary resection as possible is advisable.

SUMMARY

Broncholithiasis is a disorder that may simulate a great variety of pulmonary diseases. It may occur at any period of life but is most frequently seen in patients from 40 to 60 years of age. In our experience it was found to occur with equal frequency in men and women. In the 99 cases encountered at the Mayo Clinic and reviewed in the present study, cough, expectoration, hemoptysis and fever were the commonest symptoms. Forty-four of the 99 patients reported that they had coughed out one or more bronchial stones. Roentgenograms of the thorax may furnish the clue to the presence of a broncholith, but often they are not diagnostic. The pulmonary conditions with which broncholithiasis is most frequently confused roentgenologically are carcinoma of the lung, tuberculosis, pneumonitis, and bronchiectasis. Broncholiths occur twice as frequently on the right side as on the left.

Eighty-seven of the 99 patients in the study were examined bronchoscopically. Broncholiths were found in 38 of the 87 patients and were removed successfully in 33. In 35 patients bronchoscopy revealed abnormal findings but no stone could be visualized; in only 14 cases the results of bronchoscopic examination were completely negative.

Exploratory thoracotomy established the diagnosis of broncholithiasis in 21 cases. Resectional pulmonary operation was carried out in 38 of the 99 patients and broncholiths were found in all but four of them. Pneumonitis and bronchiectasis were the pulmonary conditions most frequently associated with broncholithiasis.

It must be constantly kept in mind that the presence of a broncholith in the lung does not exclude the possibility of other associated pulmonary disease such as carcinoma or tuberculosis.

MAYO CLINIC

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INTERESTING FOREIGN BODIES OF THE FOOD AND AIR PASSAGES

A SMALL SERIES OF CASES REFLECTING DIFFICULTY IN MANAGEMENT OR UNUSUAL CLINICAL FEATURES

V. K. HART, M.D.

CHARLOTTE, N. C.

In a sense, bringing this subject before this Society is like bringing fish to the fish market. I say this because our membership probably includes the most skillful and experienced talent to be found in the world today in this particular field of broncho-esophagoscopy.

On the other hand, our membership also represents the rank and file, viz., those of us who are doing the average day to day work in broncho-esophagoscopy. Moreover, the foreign body still remains one of our most frequent problems. Therefore, a discussion of some of the more difficult and unusual cases should be of interest to most of us.

I have picked a few such cases from a large series[1] in our clinic which have troubled or intrigued me. I dare to hope their presentation may be worth while to you.

By way of further preface, I should like to say that we reported[2] in 1932 a baby with successive bronchial foreign bodies. This is apparently quite rare.

I also had in 1945 a two-year-old child with a different foreign body in each bronchus. A piece of peanut was removed from one bronchus and a watermelon seed from the other. I thought this very unusual but Jackson[3] reported an adult with two staples and a nail

simultaneously in the bronchial tree, all of which were removed with fluoroscopic guidance. Semple and Page[4] also reported simultaneous foreign bodies in each bronchus. Multiple foreign bodies of the gastrointestinal tract are apparently more common but are usually multiples of the same object, such as pins.[5]

This introduction would hardly be complete without mentioning the excellent article by our guest of honor, Doctor Clerf,[6] on the "Historical Aspects of Foreign Bodies in the Air and Food Passages." This should be interesting to any endoscopist.

REPORT OF CASES

CASE 1. The first case presented is that of a plastic bullet impacted in the right lower bronchus of a boy aged five years. The case was referred to us on March 19, 1954, by a member of this Society who had failed in one attempt at removal because of inadequate forceps space. He had seen our report[7] of a plastic bullet removed with the aid of a bronchoscopic cautery.

As nearly as the parents could estimate, the child had strangled on a cylindrical plastic bullet about 25 days prior to admission. Chest films revealed a right basal atelectasis with some displacement of the heart to the right. He had received antibiotics which probably explained the small elevation of temperature present and his otherwise generally good condition on admission.

The parents had brought a duplicate of the foreign body. It was a cylindrical plastic bullet. It was found, as in our previous case, that the duplicate, when touched with the heated electric cautery, would melt and adhere firmly to the cautery after cooling for a few seconds. It was, therefore, decided to try this method if forceps space was inadequate.

Bronchoscopy was done on March 20, 1954, with sedation and no anesthesia. I quote my notes made at the time. "A 5 x 30 Jesberg bronchoscope was passed. After cleansing with suction, I could see the foreign body impacted in the right lower bronchus. Saline and adrenalin solution, one to five, was instilled and reaspirated. There was no forceps space whatever, even after the subsequent tissue shrinking. The cautery was then carefully advanced until I thought it had contact with the foreign body. The distance on the cautery to the end of the bronchoscope had been previously marked. The cautery was turned on briefly and then allowed to cool. The cautery

and the bronchoscope were withdrawn but I did not have the foreign body. The bronchoscope was reintroduced, the field was again cleansed by suction, the bronchoscope was advanced practically to the foreign body and the distance from the end of the bronchoscope to the foreign body measured on the suction. This was marked on the cautery and the cautery was reintroduced. After contact with the foreign body, the cautery was turned on for a few seconds, gently pushed ahead and then turned off. After allowing a few more seconds for cooling, the bronchoscope and the cautery were withdrawn with the foreign body firmly attached to the cautery (Fig. 1). Total working time 7 minutes."
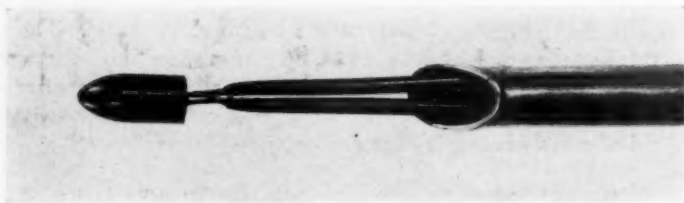

Fig. 1.—Case 1.   Foreign body firmly attached to the cautery point.

A chest film showed that the atelectasis of the right lung had disappeared. The patient was discharged two days later in good condition.

CASE 2.   I found the cautery useful in another case. The problem was again one of inadequate forceps space.

The patient was a Negress, 23 years of age, referred to me on April 1, 1953, because of a rubber cork in the right bronchus. This had been aspirated two weeks previously. An x-ray film sent with the patient revealed a foreign body in the right lower bronchus with a secondary basal atelectasis.

Bronchoscopy was done the same day. Sedation and topical cocaine anesthesia only were used. My notes made at the time are quoted from the record. "A 6 x 35 bronchoscope was passed. The left bronchus and subdivisions were normal. The foreign body was found impacted in a branch of the lower lobe bronchus with practically no forceps space. It was a red rubber stopper, making it difficult to differentiate from the mucous membranes. Adrenalin and

saline solution was used to shrink the tissues. Even then, I could not successfully get around this with any of the several types of forceps that were tried. I took the cautery and burned a small hole near the center of the cork. I was finally able to grasp the foreign body with right angle rotation forceps, one tooth on the outer edge and one tooth in the burned out area (Fig. 2), and extract it. Total working time one hour."

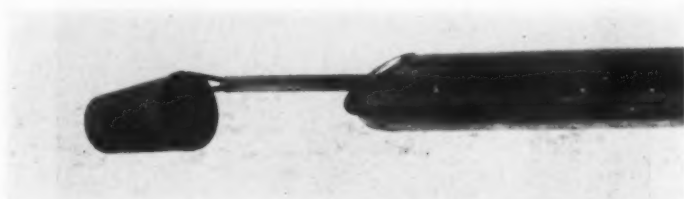An x-ray made a few days later showed no residual atelectasis. She has remained well since.

Fig. 2.—Case 2. Hard rubber stopper removed with the help of the cautery. A hole has been burned near the center of the stopper, allowing one blade of the rotation forceps to enter, while the other blade engages the margin.

Comment on Cases 1 and 2. The model of the cautery used in these cases is the same as the laryngeal cautery manufactured for years by Pilling. The only difference is in the length.

Early in my professional career, I had these made in 45 cm and 50 cm lengths for bronchoscopic use (Fig. 1). A rheostat is, of course, used to adjust the current.

It should be noted that the cautery was applied to the foreign bodies at a safe distance from normal bronchial structures. The plastic foreign body adhered so tightly to the cautery after it cooled that it was necessary to heat the cautery again to release the foreign body. Such adherence to the plastic material is, therefore, more firm than the grip of the average forceps, assuming that sufficient forceps space can be secured. The lack of forceps space prompted our use of this method.

CASE 3. The third case presented is that of a child four years of age with a .22 caliber shell casing in the left bronchus. The closed end was proximal (Fig. 3).
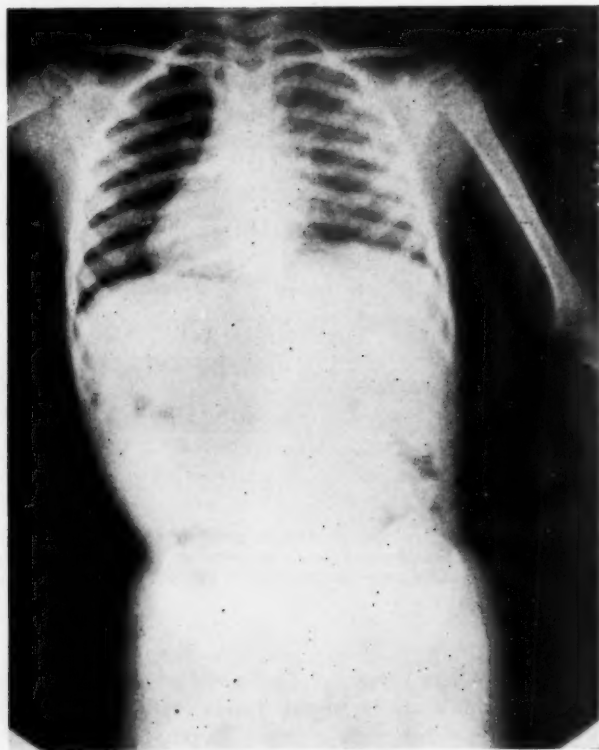
Fig. 3.—Case 3. Impacted .22-caliber shell, closed end presenting, in the left bronchus of a four year old child. The roentgenogram was made the day of aspiration, so pulmonary complications had not yet developed.

Fortunately, I saw the child on the same day the object was aspirated, January 19, 1956. Therefore, there had been no time for serious pulmonary complications to develop.

This presentation of a shell had given me trouble previously. Therefore, a preliminary tracheostomy was done. This allowed the use of a larger bronchoscope and easier control of the patient under sedation only.

Even so, despite the use of saline and adrenalin solution, I was unable to get sufficient forceps space. Several types of forceps were

used ineffectively. The operation was discontinued after I had worked almost an hour.

One of my associates, B. W. Armstrong, suggested the use of a fine wire snare. This was made by merely severing the blades from the stylet of a delicate 35 cm forceps. Two holes were then drilled, one behind the other, by a local jeweler, in the distal end of the stylet. This allowed the ends of a fine wire to be threaded through the stylet and pulled back into the cannula.

The bronchoscopy was repeated two days later. Sedation only was given. The operative notes made at the time are quoted: "A small amount of 2% pyribenzamine solution was used in the tracheobronchial tree by instillation as a local anesthetic. The tracheotomy wound was slightly enlarged and a fixation suture was placed through each side of the tracheal wall. I did this because I felt I would need plenty of room to get this foreign body through the wound. A No. 5 Jesberg bronchoscope was introduced through the tracheostomy. Secretions were aspirated and the foreign body was again readily impacted in the left bronchus. There was considerable swelling and edema of the adjacent tissues. These were shrunk by instilling one-fourth per cent neo-synephrine. The bronchoscopic snare was introduced and I was able to get this fine snare wire around the shell casing and close the snare. This gave us a very firm grip. The shell was brought against the bronchoscope and both were extracted together through the tracheostomy opening. Following removal of the foreign body, the bronchoscope was reintroduced and retained secretions aspirated from the lower left bronchus. The tracheostomy tube was replaced purely for purposes of drainage. The total working time was about ten minutes."

After the tracheostomy and first bronchoscopy, she developed moderate fever. The pulmonary infection was controlled by a daily intramuscular injection of 400,000 units of penicillin for six doses. She was decannulated on January 23, 1956, and discharged on January 24, 1956, in good condition with a normal blood count.

Comment. As intimated above, I had had difficulty previously with this identical foreign body. I well remembered a shell casing impacted (closed and presenting) in a bronchus. I was not able to extract the foreign body until the fourth attempt. In that case I used a double pronged Jackson forceps with the points filed down. I also used this same modified forceps in solving a like situation in

another case. This was an 11 year old boy who had the firing cap of a
12 gauge shotgun shell impacted in the left lower bronchus despite
four previous bronchoscopic attempts at removal by the endoscopist
who referred the patient for consultation.

The snare used in the case presented was useful and efficient. I
doubt that we are original in the use of a bronchoscopic snare, al-
though this instrument is not listed in the current surgical catalogues
reviewed.

I have for years used a laryngeal snare. I do not know the name
of the company that made it. One of the things for which I have
found this snare useful was in the removal of toy jacks from below
the cricopharyngeus. I stumbled on the idea one day after I had tried
unsuccessfully for about half an hour attempting the method orig-
inally advised by Chevalier Jackson[8] of covering one of the ball points
with cupped forceps. It suddenly occurred to me that if a wire snare
was looped around one of the ball points a secure grip would be
obtained but one that would allow this dangerous foreign body to
dangle from side to side without injury to the esophagus.

CASE 4. The fourth case chosen for presentation is interesting
in that a second foreign body resulted from the removal of a nail
from the right bronchus of a child aged two and a half years.   The
referring endoscopist in manipulating the nail with side-curved bron-
choscopic forceps had broken off one of the blades. After the nail
was removed with other forceps, the blade was found by x-ray to be
in one of the lower lobe branches. He was unable to visualize the
same and referred the child to us for fluoroscopic aid.

On arrival at our hospital on February 18, 1946, roentgenograms
revealed the blade to be apparently in one of the posterior subdivisions
of the right lower lobe (Fig. 4). The baby had had a tracheostomy
before coming to us.

Therefore, a bronchoscopy was first done through the tracheos-
tomy opening, using a 3½ mm Jackson bronchoscope. Sedation
was given but no anesthesia was used. The foreign body could not be
visualized.

The patient was then moved to the x-ray room. The operative
notes made at the time are quoted. Although these notes do not
state the type of forceps used, my recollection is that they were small,
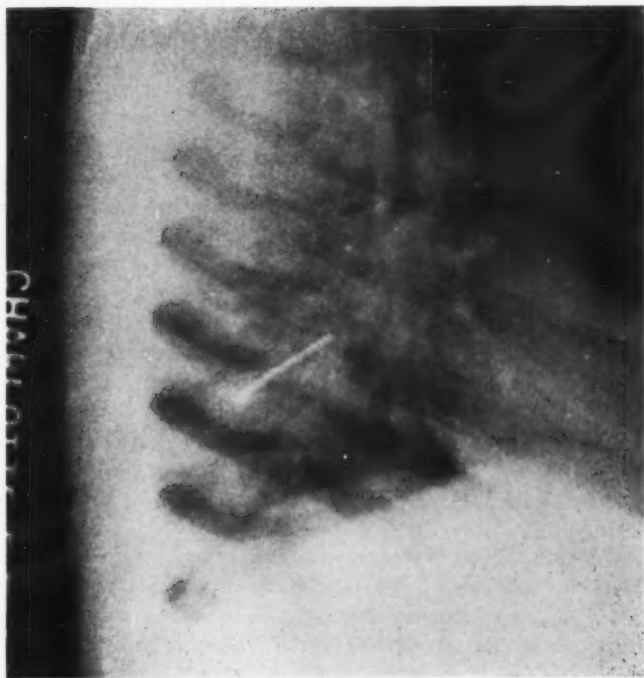
Fig. 4.—Case 4. Lateral view showing broken bronchoscopic forceps blade in posterior branch bronchus of right lung. Removed with the aid of triangulation fluoroscopy.

delicate, side-curved forceps. "A 3½ mm Jackson bronchoscope was reintroduced through the tracheostomy opening. Using triangulation fluoroscopy, we were able to identify the correct bronchial subdivision; and, after working about half an hour, I was able to seize the broken piece. However, the first seizure was too near the mid-portion and the foreign body could not be safely withdrawn. It was then released and re-seized near the end and withdrawn. It proved to be one whole blade, as indicated in the x-ray." Uneventful recovery followed.

Comment. The whole subject of triangulation fluoroscopy in the removal of foreign bodies beyond bronchoscopic vision has been amply covered by my associates, W. E. Roberts and A. A. Dorenbusch.[9] Therefore, there is little for me to add. I can only emphasize

that over the years it has been of great help to us.   Our successes have considerably outnumbered our failures.   It has the simplicity of the single screen, the plane of which does not have to be changed. The cost of installation is also much less, when compared with the modern biplane fluoroscope or the newer stereoscopic fluoroscope.

This discussion would not be complete without reference to the article on biplane fluoroscopy by Jackson and Chamberlain.[10]   This is not only an excellent historical review of the subject but cites the great improvements in the mechanics of biplane fluoroscopy which have brought it to a high degree of efficiency.

More recently the reports of Alden H. Miller[11] have called attention to the stereoscopic fluoroscope.   This gives three-dimensional fluoroscopy which, of course, is ideal.

In the final analysis, there is great dependence on the radiologist and his choice of equipment. Other factors determining that choice are the need for the same in a particular hospital or clinic and the financial resources available.

CASE 5.   This case is the story of the strange journey of an open safety pin in a ten months old baby.   The thoracic surgeon, Doctor Julian A. Moore, of Asheville, North Carolina, who referred this patient to me, has kindly given me permission to use his hospital record of the case for reference.

The survival of this baby is a great tribute to his surgical skill and the pediatric care.

I did no instrumentation on this baby except a diagnostic insertion of an alnico magnet.   The story, however, is such an interesting and unusual one that I think it will be of great interest to all endoscopists.

Doctor Moore first saw this baby with an open safety pin in the esophagus, point up, on October 8, 1950.   Under ether anesthesia, an esophageal speculum was passed and twice an effort to remove the pin by the point sheathed method was attempted.   Each time the pin became disengaged at the cricopharyngeus.   The pin then slipped down into the lower esophagus and an attempt was made, unsuccessfully, to take the pin into the stomach.   The operation was then discontinued.

The following day the child was again put to sleep under ether anesthesia. An esophagoscope was passed. The pin was found in the lower esophagus. The hinge was grasped with dangling forceps and an effort made, unsuccessfully, to take the pin into the stomach. After a few minutes, the procedure was abandoned.

The following day the baby was sent to me for consultation. On October 11, 1950, anterior-posterior and lateral roentgenograms led us to believe the pin was in the intestinal tract (Fig. 5 a, b). Moreover, a duplicate of the pin brought by parents showed this to be magnetic.

Therefore, to give us further assurance that the safety pin was not in the stomach, an Equen alnico magnet was passed through a laryngoscope without anesthesia under fluoroscopic guidance. The stomach was gently inflated with air and the stomach explored. Even when the magnet was seemingly close to the pin there was no magnetic response. It was assumed, then, that the pin was in the intestinal tract.

The following day, x-ray films showed the pin in the same position. The temperature was 102 (rectal), the white count 19,000, with some secondary anemia. There was no clinical evidence of a mediastinitis.

Three hundred thousand units of penicillin was given intramuscularly on the day of admission with a 250 mgm suppository of terramycin. The terramycin suppository was repeated every 12 hours and the penicillin every 24 hours through the day of discharge on October 13, 1950.

X-rays taken on this latter date revealed no change in the position of the safety pin. We felt that time should be given for natural passage of the foreign body, although we were disturbed by the fact that the pin was apparently impacted. I did not think, at the time, of attempting to get an Equen alnico magnet into the intestinal tract. As events developed, such would have done no good anyway. The baby was returned to the care of Doctor Moore.

On readmission to Doctor Moore's service, x-ray examination confirmed our impression that the pin was in the upper abdominal cavity and in the same position. It was thought to be impacted in the third portion of the duodenum.
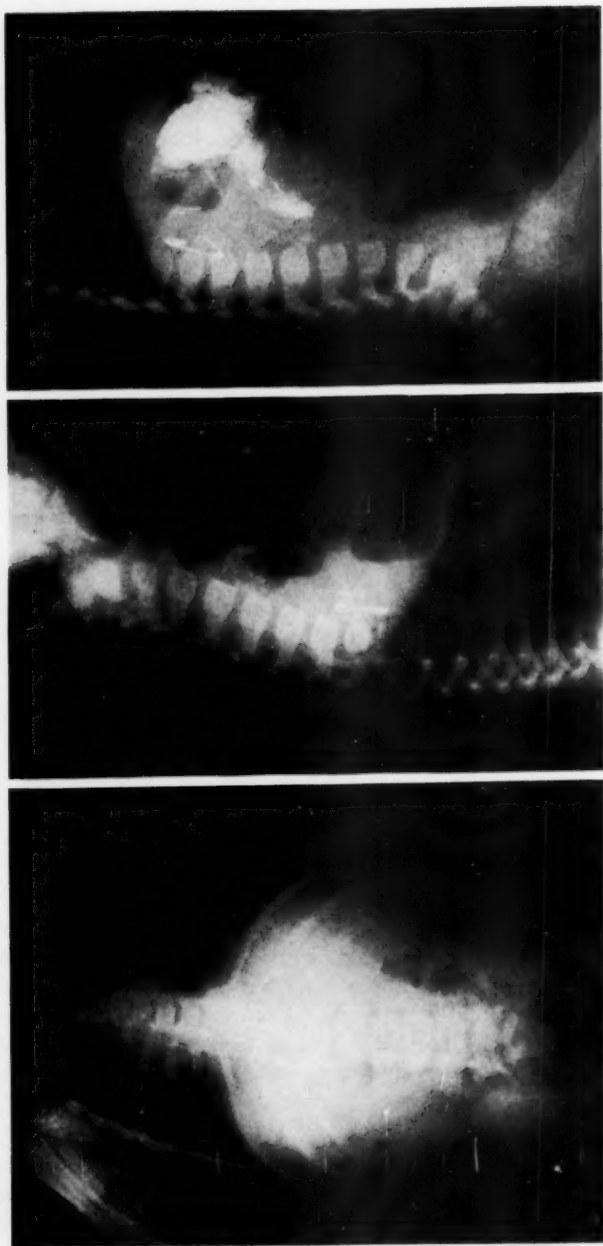
Fig. 5.—Case 5. (a) Anterior posterior view of open safety pin in ten months old baby. It looks as though it might be in the stomach. (b) A lateral view suggests pin is not in stomach but in duodenum. (c) Barium study suggesting pin is outside the gastro-intestinal tract. Although the pin seems to be below the diaphragm, it was later removed from the posterior mediastinum.

Exploratory laparotomy on October 14, 1950, by Doctor Moore failed to reveal the pin. Subsequent comprehensive fluoroscopic and x-ray study of the esophagus and gastro-intestinal tract with ingested barium and barium enema on October 20, 1950, revealed the pin to be outside the gastro-intestinal tract, behind the stomach, just to the left of the mid-line over the 12th thoracic vertebra (Fig. 5, c). It was noted that the pin had not changed position.

On October 24, 1950, the abdomen was reopened through the old incision by Doctor Moore. The lesser peritoneal cavity was searched without result. The esophagus and vertebral column were palpated but no pin felt. However, when Doctor Moore inserted his finger through the hiatus of the diaphragm he thought he could feel the pin. The condition of the patient compelled cessation of the operation.

The baby rallied and did well for one year. She was readmitted to the service of Doctor Moore on November 25, 1951, because of hematemesis. A roentgenogram revealed that the position of the pin had not changed.

Transfusion preliminary to thoracotomy was done with continuing transfusion during the operation. Doctor Moore could feel the pin in the posterior mediastinum above the diaphragm on the body of the 12th vertebra. It was removed by sharp dissection with very little bleeding. The posterior wall of the esophagus was somewhat blue in color but no leak or defect was demonstrated.

Uneventful convalescence followed. The patient was last seen in 1957, six years later, and was doing well.

Comment. Our x-ray films misled me, and our own radiologist. We thought the pin was in the upper abdominal cavity and probably in the duodenum. This was apparently also the opinion of the radiologist in Asheville. None of us suspected that the pin was in the posterior mediastinum above the diaphragm.

This misinterpretation can be explained by the dome shape of the diaphragm. Thus the pin could be just above the posterior border and still appear to be below the crest of the diaphragm, as seen on the x-ray films.

There is one striking feature. The pin never changed position from the time we first saw the baby. This strongly suggests that the pin was already in the mediastinum.

The baby had a barium study after leaving our hospital.   No leak in the esophagus was shown.

Thus the defect in the esophagus must have closed spontaneously, despite the fact that it must have been large enough to allow the keeper to go through.   Moreover, there were no clinical signs of a mediastinitis.   However, antibiotics given might well have been a factor in preventing such signs.

Clerf[12] reported perforation of the esophagus in three cases without a mediastinitis.   In one, death followed due to perforation of the pericardium and ventricle.   A second safety pin was removed but death followed 14 days later as a result of hemorrhage from the innominate artery.   In a third case, barium showed the point through the esophagus.   The pin was removed by endogastric version followed by recovery without complication.

Holinger and Johnston[13] report another interesting case with perforation.   An open safety pin in the hypopharynx of an infant caused hemorrhage and was removed endoscopically.   The spring end was in the cervical esophagus.   Six months later, the child developed an aneurysm of the carotid artery which ultimately proved fatal.

The hematemesis one year later must be explained.   I think it can only be assumed that the point of the pin engaged the wall of the esophagus in the act of swallowing and punctured a vessel.   The fact that the child recovered and remained well over a period of six years means that one of the larger arteries was probably not involved.

Stein and associates[14] reported an aortic-esophageal fistula with fatal hemorrhage 19 days after ingestion of a fish bone.   They were able to find 80 similar cases in the literature.

The outcome in this case, then, may well be considered remarkable.   Nevertheless, I think the sequence of events emphasizes the importance of fluoroscopic guidance in handling these safety pins which lodge point up in the esophagus.   This is particularly so if the pin is magnetic, because of the ease and safety of manipulation of the alnico magnet even in a small infant.[15]

Clerf[16] states that biplane fluoroscopy is essential in dealing with such safety pins in the thoracic esophagus or stomach.   Jackson[17] also states that fluoroscopic aid is indicated in practically all cases of safety pins.

Since the advent of the alnico magnet, we agree with Equen[18] that the average magnetic foreign body of the gastro-intestinal tract can be handled satisfactorily with a single tube fluoroscopic apparatus. Unfortunately, all safety pins are not magnetic.

Norris[19] reported the use of a sheathed ring forceps without esophagoscopy in such cases. Lell[20] gave an excellent paper before this Society last year on a similar method with a flexible forceps. Such techniques, of course, require special fluoroscopic apparatus for forceps manipulation.

CASE 6. This case is of much interest because this young lady, of 16 years, swallowed a clinical thermometer. She had ingested it while a patient in the infirmary of a nearby girls' college when the nurse was taking her temperature.

It had been in the stomach 48 hours when I was called in consultation. I advised that an effort first be made to remove the foreign body by endoscopy.

This patient was seen on November 5, 1937. Sedation and topical cocaine anesthesia were used. The operative notes are quoted. "Patient was sent to the x-ray department. A large 22 inch Mosher esophagoscope was passed. The triangulation fluoroscope was used, showing the thermometer in the fundus of the stomach. Under fluoroscopic guidance, I was able several times to seize the shaft with large side-curved Tucker tack forceps. However, the end was abutting against mucous membrane and we were unable to dislodge it. The esophagoscope was then closed with a glass covered cap and the stomach inflated with air, throwing the mucosa away from the end of the foreign body. By repeatedly using this inflation and with the help of the fluoroscope, I was finally able to get the large end in the bronchoscope with Tucker tack forceps and extract it. Time one hour and 15 minutes."

Comment. We at least learned the temperature of the stomach. The thermometer registered 101 degrees on removal.

We have not used the Mosher esophagoscopes for years. We feel the Jackson and Jesberg esophagoscopes are much safer. Nevertheless, in this instance, the large oval mouth of the Mosher instrument was a distinct advantage.

SUMMARY

A small series of foreign bodies of the food and air passages has been presented. These were chosen from a large group because of difficulty in management or unusual clinical features. The electric cautery was useful in solving two bronchial impacted foreign bodies, one a plastic bullet and the other a rubber stopper. A bronchoscopic snare was very useful in removing a shell casing, closed end presenting. The role of triangulation fluoroscopy was discussed in removing a small forceps blade beyond bronchoscopic vision. The fifth case cited the passage of an open safety pin through the esophagus of an infant and removal successfully one year later from the mediastinum. Two laparotomies had been previously done because the pin was thought to be in the upper abdomen. The sixth and last patient presented had swallowed a clinical thermometer which was removed endoscopically from the stomach.

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After this paper was written, the following modification of triangulation fluoroscopy was found in the foreign literature: Van Hellemond, K., and Waar, C. A. H.: Use of Parallax Fluoroscopy in Bronchoscopic Extractions of Corpora Aliena in Lower Respiratory Tract. Acta Otolaryng. 42:460-464, 1952. A single tube is used beneath the table moving in a transverse manner.

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EXPERIENCES WITH DILATATION OF THE ESOPHAGUS FOLLOWING SURGERY FOR ESOPHAGEAL ATRESIA

Lewis E. Morrison, M.D.

Indianapolis, Ind.

A review of the records at the Indiana University Medical Center shows that the first congenital tracheo-esophageal fistula patient diagnosed *ante mortem* was admitted to the hospital in July, 1939. In immediately succeeding years there were only a few such diagnoses made. The surgical treatment was ineffective and there were no survivors. Vogt[51] said in 1929 that "some ingenious surgeon would eventually devise a cure."

In 1670 Durston[17] first recognized esophageal atresia. Tracheo-esophageal fistula was actually described and proven by autopsy in 1696 by Gibson.[27] The recorded possible means of cure appeared in 1869, but it was early in 1900 before the first attempt by Richter was made to close the fistula.[6] In 1929 Mixter[31] exposed the esophagus via the posterior extrapleural approach. Interest heightened as more cases were operated upon with increasing aptness and boldness. End-to-end anastomosis was advocated as the best treatment when possible, and ligation of the fistula and exteriorization of the proximal pouch when anastomosis was not possible. Levin and Ladd, at separate hospitals, successfully operated upon and saved infants with tracheo-esophageal fistula with atresia in 1939 by constructing a subcutaneous esophagus. These were the first patients with this disease to survive and there was only a single day's difference in the age of the patients![32] In 1941 Haight[18] of Ann Arbor reported the first successful outcome of an esophageal anastomosis.

EMBRYOLOGY

The trachea is first manifest as a thickening of entodermal cells on the ventral surface of the esophagus in the three millimeter embryo.

As the embryo increases to four millimeters, the trachea buds off the esophagus; at nine millimeters, it begins to bifurcate (Fig. 1).

During this phase of development (six to eight weeks of intra-uterine life) the lining of the esophagus proliferates and obliterates the lumen. Soon vacuoles appear within the esophagus and re-establish the lumen by coalescing.[2,29]

Gruenwald[15] explains the formation of a fistula by saying that the laryngotracheal tube fails more or less completely to separate at the proper time from the esophagus. The atresia of the esophagus is due to the fast growth of the trachea before it completely separates, drawing out the party wall of the esophagus and trachea.

Ladd and Swenson[33] postulate that failure of the mesoderm to separate the trachea from the esophagus accounts for the tracheo-esophageal fistula and that failure of the vacuoles to coalesce accounts for the esophageal atresia.

Fluss and Poppen[13] introduce the concept that pressure exerted by anlage of the heart or abnormal vascular system vessels may cause the abnormality.

Ferguson[12] uses the Keith and Spicer theory of development of the anomaly saying that the fistula is established in the six millimeter to eight millimeter stage (seventh to eighth week of fetal life). The eleven millimeter embryo will either have a normal trachea and esophagus, or the fistula will be present.

Current experiments, and experiences with congenital diseases of other organs of the body, indicate that stress occurring in the mother is a major factor in producing tracheoesophageal fistula.

CLINICAL EXPERIENCES

At our institution these cases of tracheo-esophageal fistulae were operated upon by members of the general surgery department; post-operative dilatations were handled by members of the broncho-esopha-gology department.

In 1946, after four failures, the intrathoracic repair of a tracheo-esophageal fistula was successful and this patient is alive and well today. The management of patients with tracheo-esophageal fistulae has become more successful as medical science progresses. Where the
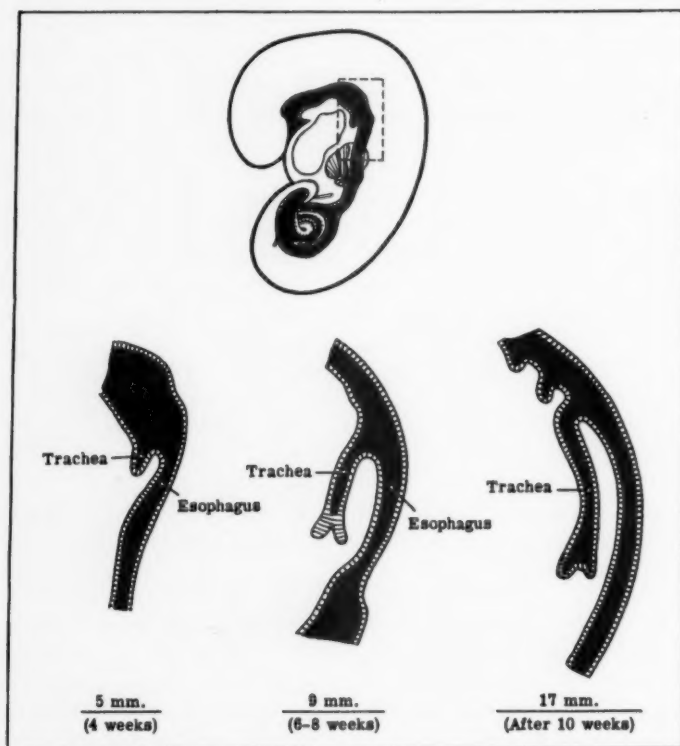
Fig. 1.—Illustrating normal development of the trachea and esophagus, after Arey.

chance of survival in the 1940's was extremely poor, the outlook now is quite hopeful. Earlier diagnosis, advances in anesthesia, control of infection with antibiotics, refinement of surgical technique, and improved pre-operative and postoperative management have played the major roles in saving these infants. As more children survive the surgery, more postoperative complications have been seen.

Even though the surgical repair was done over a fairly large sized catheter, it was soon evident that the site of esophageal anastomosis did not maintain a lumen. Children surviving the surgery became sick in about two weeks. They were unable to eat, developed pneumonitis, lost weight, and contrast studies or esophagoscopy showed

obstruction at the site of esophageal surgery. A gastrostomy was necessary to maintain nutrition. Subsequently, a string was passed and the gastrostomy was also used for retrograde dilatations with Tucker bougies.

After several patients in whom a gastrostomy was done one to three weeks after anastomosis and repair of the fistula, the surgeon began to do the gastrostomy while the infant was awakening from the anesthetic. It became evident that this additional bit of surgery was unnecessary at the time and made the chance of recovery more precarious. Therefore, the gastrostomy surgery and the insertion of a nasogastric string was postponed until a day or two following surgery. This procedure has proved to be the best plan.

The gastrostomy has several advantages. First, it permits early feeding with protection of the esophageal suture line. Prolonged intravenous fluids are not necessary. Second, it provides an avenue for the nasogastric string which maintains a lumen in the esophagus and permits later esophageal dilatations. Oral feedings are begun on approximately the seventh day and the child is soon taking all foods by mouth with the gastrostomy maintained only for the purposes of dilatation.

The early cases were dilated after the second or third postoperative week. The method of management was based on the experience of treating caustic injury of the esophagus and there was fear of perforating the esophagus at the site of anastomosis. Patience and caution characterized the program. The dilatations were done weekly with Tucker bougies used in a retrograde manner starting with size twelve French. The size was increased very slowly and by six months size 18 Fr., or perhaps 26 Fr., was reached. Increases in size after six months were sporadic and sometimes no dilatations were done for months at a time. The gastrostomy usually was maintained from 12 to 18 months. After it was closed a Hurst dilator (size 30, 32 or 34 French) was passed about once or twice a year to measure the size of the esophagus.

The program was satisfactory in that the children were able to take food by mouth and the esophageal lumen was maintained. There was only one instance of mediastinitis following dilatation and this patient recovered promptly.

The program was not entirely satisfactory in that there was trouble from the indwelling gastrostomy tube. After several months,
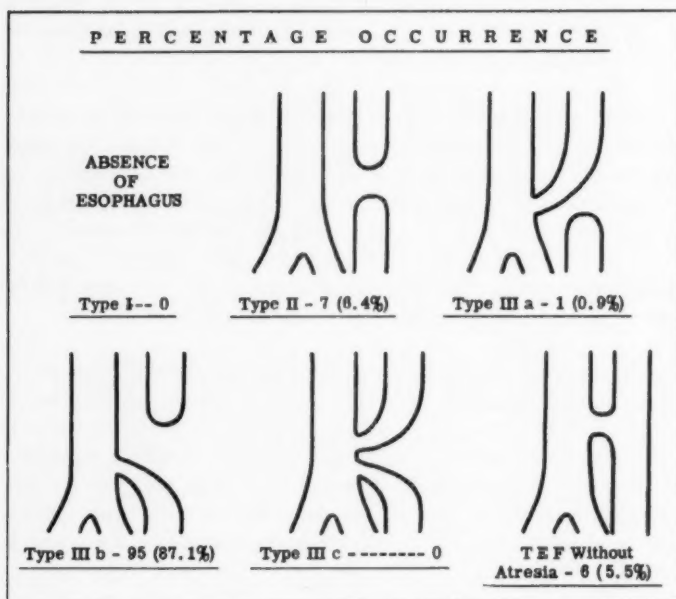
Fig. 2.—Diagram illustrating Vogt Classification of esophageal anomalies
with the number of cases and percentage occurrence.

the problem of leakage around the tube often became severe.   There
were excoriation of the skin of the abdominal wall, loss of food and
fluids, dehydration, electrolyte imbalance, anemia and malnutrition.
Symptoms progressed in spite of preventive measures such as liberal
applications of Lassar's paste, the use of larger and larger gastrostomy
tubes, frequent dressing changes, and surgical tailoring of the gastros-
tomy wound.   Two of these problem patients progressed to the point
where it was necessary to close the gastrostomy, following which
there was dramatic clinical improvement.   Two other patients died.
One of these had many other anomalies which undoubtedly contrib-
uted to her demise.   The other death, however, can be attributed
directly to disease caused by the gastrostomy tube.   At no time did the
nasogastric string cause trouble.

The early gastrostomy and nasogastric string procedure was not
followed ten times in this series of over a hundred cases.   Four of these
patients were treated very early in our experience and a gastrostomy

was not done; these four infants died. The other six patients in whom the gastrostomy was delayed all developed complications: The first infant died on the tenth postoperative day from the aspiration of a feeding. The second infant had an esophageal lumen of one centimeter two weeks postoperatively as seen with the esophagoscope. A gastrostomy was done. Four weeks postoperatively there was "only a dimple" seen endoscopically. The stricture was reoperated upon two days later, but the child died six weeks later; the cause of death was fluid and electrolyte loss from diarrhea and gastrostomy leakage.

The third infant was operated upon by a different surgeon. A gastrostomy was not done and the child was apparently well and released to home care in two weeks. The patient was brought back five weeks postoperatively and a feeding gastrostomy was done because of stenosis. This child died a week later while being esophagoscoped.

The fourth infant developed stenosis two and one-half weeks postoperatively and a feeding gastrostomy was done. A week later retrograde dilatations were begun. In the fourth postoperative week, the suture line was ruptured during a retrograde dilatation. (This is the only instance in this series in which rupture of the esophagus occurred.) Surgical management of this complication was successful. No further dilatations were performed, and a mild stenosis was first manifest three years later. It was managed without difficulty.

As a result of our early experience with this disease, the surgeon decided that early gastrostomy and nasogastric string insertion should be a part of the postoperative management. Three and one-half years after this routine was established, there was an infant with large proximal and distal pouches which overlapped each other. One would think that an anastomosis would be uncomplicated; therefore, the surgeon did an anastomosis and repair of the fistula, but did not perform a gastrostomy. An esophagogram using lipiodol was done several days later and there was normal repair. Water and then formula by mouth were given. In about two weeks the infant began having trouble with feedings, and an esophagoscopy revealed a stricture at the anastomosis. Peroral dilatations were done at weekly intervals to maintain a lumen. It was necessary to use a firm red rubber catheter as the more flexible Salzer shot-filled dilators would not pass. After three months of difficulty maintaining a lumen of 20 Fr., there was an unexplained relaxation of the stenosis and a Hurst mercury filled bougie (26 Fr.) passed with ease. The dilatations were continued; when the child was six months of age, a 36 Hurst bougie was passed

with ease. This size, or larger, has been used for three years to measure the lumen.

Three months after the above experience another anastomosis was performed and a gastrostomy was not done. Two weeks postoperatively obstruction to swallowing occurred. Dilatations were attempted, but were unsuccessful. A gastrostomy was done. Three weeks later the stricture was reoperated upon and a nasogastric string inserted for dilatations. An uncomplicated recovery occurred, including retrograde dilatations.

As a result of these experiences in mid-1955, the gastrostomy and nasogastric string have become a routine part of the postoperative program. Dilatations are begun at the discretion of the surgeon. There have been prolonged courses of dilatation, and there have been difficulties as a result of the gastrostomy, but re-operation has not been necessary for correction of a stricture. There has been no difficulty from the indwelling string and there has been no instance of mediastinitis resulting from dilatation except once as described above.

Based on our series, infants operated upon for tracheo-esophageal fistula with esophageal atresia have trouble from a stricture at the site of anastomosis two to five weeks postoperatively.

The program for postoperative dilatation has evolved to the following: at approximately two weeks or later after esophageal anastomosis, the esophagus is dilated with Tucker dilators in a retrograde manner. This is done several times at three day intervals, beginning with size 12 Fr. and increasing to whatever size fits snugly in the esophagus. Usually the child leaves the hospital after four or five such dilatations. The dilatations are then done at weekly intervals on an outpatient basis. Tucker bougies are routinely used pulling the dilators through the gastrostomy and out the mouth; however, occasionally the dilators are started through the mouth and pulled out the stomach.

With the problems which gastrostomy tubes cause clearly in mind, we attempt dilatations from above as soon as feasible. These are done with Salzer or Hurst dilators while the nasogastric string is still in place. As soon as it is evident that the lumen can be maintained by dilatations from above, the nasogastric string is removed and the gastrostomy is allowed to close.

A further refinement of the nasogastric string method of handling the postoperative dilatations has been developed by Dr. Jack D.

Summerlin. The gastrostomy tube came out of a child who had been released from the hospital. The parents did not re-insert the tube. When he returned for dilatations, the gastrostomy wound had closed around the nasogastric string, thereby preventing a Tucker retrograde dilatation. A single Tucker bougie was pulled through the mouth, esophagus and stomach down to the narrowed gastrostomy; the bougie was then withdrawn through the mouth. Larger size bougies were then passed one at a time in this manner. This method of management has the advantage of a guided dilator and none of the disadvantages of the gastrostomy tube. There is minimal loss of fluids through the gastrostomy opening with no excoriation of the skin; a band-aid is sufficient dressing. This method has been used only a few times, but it shows much promise and will be the subject of further study.

<div align="center">STATISTICAL STUDY</div>

This series begins in July, 1939, and ends in July, 1958. This study covers 109 patients with congenital esophageal anomalies. Forty-three of these patients of ages ranging from seven months to twelve years are alive.

Analyzed according to Vogt Classification,[51] the cases occurred as follows:

Type I	0
Type II	7
Type III a	1
Type III b	95
Type III c	0
Tracheo-esophageal fistula	
without atresia	6
Total cases	109

The frequency of occurrence of the different types of esophageal lesions in this series is comparable to that in other studies.[11,21,38,47]

Type I (complete absence of esophagus) did not occur in this series.

Type II (atresia of the middle portion of the esophagus or the upper and lower segments of the esophagus ending in blind pouches) occurred seven times in 109 patients or 6.4 per cent.

Type III a (the upper pouch entering the trachea and a blind lower esophageal pouch) occurred once in 109 patients or 0.9 per cent.

Type III b (the upper esophagus being a blind pouch and the lower esophagus entering the tracheobronchial tree) occurred 95 times in 109 patients or 87.1 per cent.

Type III c (the upper esophagus and lower esophagus entering the tracheobronchial tree) did not occur in this series.

There were six patients with tracheoesophageal fistula without esophageal atresia or 5.5 per cent.

There were seven patients with atresia of the middle portion of the esophagus without tracheoesophageal fistula. One of these survived surgery.

There were 96 patients with tracheo-esophageal fistula with atresia of the esophagus (classes IIIa and IIIb). Thirty-seven of these patients are alive today. Some of the infants were not operated upon as they were never in condition to undergo surgery. Many others were in dire condition when surgery was performed. Of the 59 infants who died, 16 had other congenital anomalies which were incompatible with life, such as imperforate anus, atresia of the duodenum, and serious congenital heart defects. Five patients with such diseases were operated upon and lived through both operations.[3]

There were six infants with tracheo-esophageal fistula without atresia of the esophagus. Three were diagnosed and operated upon soon after birth. One was diagnosed and operated upon at the age of one year; another was diagnosed and operated upon at the age of two and one-half years. The diagnosis in the sixth infant was made at autopsy. The five infants who had surgery survived and did not require postoperative esophageal dilatation.

The incidence of esophageal congenital anomaly has been estimated to be from one in 800 live births[4] to one in 10,000 live births.[27] Haight analyzed the incidence of occurrence by five year periods and found the extremes of one in 1,469 in the years 1935 to 1939, to one in 15,432 in the years 1945 to 1949.[17]

The incidence of occurrence of tracheo-esophageal fistula without atresia in this series is 5.5 per cent which is higher than Swenson's 1 per

cent,[49] the 3 per cent usually given,[16,31,35,41] but lower than Cardelle and Berens' 10 per cent[9] and Abbott and Hopkins' 15 per cent.[1]

The percentage relationship of other types is also similar to other authors' experience as regards type II and III b.[14,23,28,34]

The rate of recognition of congenital esophageal anomalies is obviously influenced by the education of physicians and nurses with respect to the symptoms of the disease. In our institution there were no diagnoses made prior to 1939. There were five diagnoses in the five year period, 1939 to 1944. Twenty-one were diagnosed in the next five year period, and 48 in the next five year period.

THE DILATATION PROGRAM

As a generalization, it can be said that 70 per cent of the infants have had less than 12 dilatations during the first few months of life. After that, they have an adequate esophageal lumen which increases as the child grows.

Twenty-four per cent of the infants have had dilatations for a longer time. These were done at approximately monthly intervals; after approximately a year, the lumen was well established.

Three infants (6%) have required prolonged treatment. One child had 41 retrograde Tucker dilatations in 15 months; he was then dilated once monthly until two years of age in order to reach and keep a lumen of 30 Fr. One child had 47 retrograde Tucker dilatations in 18 months. A shelf-like obstruction developed at the anastomosis. Dilatation with Hurst and retrograde Tucker dilators was continued every month or so to maintain a lumen of 30 Fr. When the child was three years old, the string was removed; the lumen has increased with growth to size 36 Fr. She is now five years old. The third child is the sole survivor of surgery for atresia of the esophagus without tracheo-esophageal fistula (Type II). She is now three and one-half years old with a "shelf" at the anastomosis. She had 92 Tucker retrograde or combination Hurst and Tucker retrograde dilatations. Because the gastrostomy was causing much difficulty, it was allowed to close a year ago. Since then the size of dilator which would pass has varied from 16 to 30 Fr. There has been no dysphagia.

The possibility of stricture formation at the site of anastomosis was mentioned even before the first successful anastomosis was performed on a patient with esophageal fistula.[34] The first successful

anastomosis did develop a stricture which required dilatation.[18] Eleven
authors indicate stricture formation is common and requires dilatation.
Others indicate stricture occurs, but is not common, while still other
authors do not mention stricture or dilatations.

None of the above authors have found dilatations mandatory
postoperatively in every instance of esophageal atresia as has been our
experience, although it may be necessary occasionally.

A Hurst dilator of size 34 Fr., or larger, has been passed at 6
to 12 month intervals on a number of children. Seven patients have
been followed five years; two patients have been followed six years;
and one patient has been followed eight years. We believe that once
the lumen is established, it will grow with the child.

It has been the experience of our group and others that the
esophagogram may show a severe deviation from the normal pattern
and yet the child can eat satisfactorily. It is often stated that the
act of normal swallowing is the best dilator for this type of esophageal
stenosis. This seems to be true after a satisfactory lumen is established.

UNUSUAL COMPLICATIONS AND EVENTS

In 1950, a two and one-half year old child began coughing when
she took fluids. Even though a recurrent fistula was suspected and
demonstrated by x-ray, she died before surgery was done. Autopsy
confirmed the recurrence of the fistula below the narrowed esophagus
at the site of anastomosis. This is the only child in whom there was
a recurrence of the fistula. The percentage in other authors' cases
is approximately the same.[14,17,36]

One child who died following surgery for tracheo-esophageal
fistula was the third child in one family to die of this disease. Sloan
and Haight[47] have collected the known cases in siblings. Hausmann,
Close and Williams[19] have also recorded three consecutive siblings with
esophageal anomalies.

It is stated by many authors that breakdown or leak at the site of
anastomosis leads to postoperative stricture. In this series, none of
the four who survived this complication developed serious trouble
with stricture formation. In one infant a few dilatations were done
and the lumen was adequate thereafter. Another case already men-
tioned required some dilatation three years postoperatively. The
remaining two had no dysphagia and did not require dilatations.

Five patients have had foreign bodies removed from the esophagus. These include buttons, coins, and meat lodged above the site of anastomosis. One child whose parents are both blind has had several foreign bodies removed.

THE SIZE OF THE ESOPHAGUS

The size of the lumen of the normal esophagus of an infant or child of any age is not known. With an attitude of cautious curiosity and investigation, we have found it possible in many instances to pass a 36 Fr. Hurst on six month old infants who have had end-to-end anastomoses. It is true that this extreme size causes respiratory obstruction from pressure on the larynx and trachea, but the large dilator is merely passed in and out quickly to measure the lumen and no ill effects have been noted.

SUMMARY AND CONCLUSION

This is a study of 109 congenital lesions of the esophagus. The embryology is discussed. The cases are analyzed according to the Vogt classification.

The development of the intrathoracic repair of the fistula and end-to-end anastomosis of the esophagus has resulted in the saving of many lives. The site of the end-to-end anastomosis of the esophagus probably will develop a stricture. This stricture is a threat to the successful outcome.

Early insertion of a gastrostomy and nasogastric string is advantageous and usually necessary in the postoperative management. The indwelling gastrostomy tube is the source of much difficulty and should be removed as soon as possible. The nasogastric string has caused no trouble.

Retrograde dilatation with Tucker bougies is a safe and satisfactory manner of early dilatation. Passage of Hurst or Salzer bougies will maintain or enlarge the esophageal lumen. The dilatation programs of the past and, also, the current dilatation program are described.

It is feasible to allow the gastrostomy opening to stenose around the nasogastric string. The string can then be used for safe dilatation with Tucker bougies from above, but without the difficulties and complications of a gastrostomy tube.

Infants who have end-to-end anastomosis of the esophagus require postoperative dilatations to prevent stricture formation. In this series, 70 per cent have had minimal trouble, 24 per cent have had moderate trouble, and six per cent prolonged trouble and care of their postoperative stricture. Other authors' experience with stenosis and dilatation is recorded.

After a satisfactory lumen is established, it is not necessary to continue dilatations. The lumen at the site of anastomosis increases in size as the child grows.

Leak or breakdown at the site of anastomosis does not necessarily cause stricture formation.

A family with three children having congenital esophageal disease is mentioned.

Esophageal foreign bodies have been removed from five children in this series. Other complications are described.

Recurrence of tracheo-esophageal fistula is an uncommon complication.

Tracheo-esophageal fistula without atresia of the esophagus does not require postoperative dilatations.

It is possible to pass a 36 Fr. Hurst dilator through the esophagus of a six month old child. The size of the lumen of the normal esophagus is not known.

603 HUME MANSUR BLDG.

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SHOULD PATIENTS BE HOSPITALIZED FOR PERORAL ENDOSCOPIC PROCEDURES?

CHEVALIER L. JACKSON, M.D.

PHILADELPHIA, PA.

During the course of casual conversation among a group of Philadelphia endoscopists this question arose, and there seemed to be so much difference of opinion that I deemed it worth presenting, with the thought that it would prove interesting and that some helpful exchanges of views might be stimulated. I shall first outline the policy we follow at the Temple University Clinic, with some comment, and mention the views of some of our Philadelphia colleagues.

Let me begin by saying that we definitely do not hospitalize all patients for any of the three procedures with which we are concerned: direct laryngoscopy, bronchoscopy or esophagoscopy. We do not always admit a patient for even his first endoscopy, though we do admit a good many, for various reasons. Let me now consider our indications for admission of the patient especially for the endoscopic procedure.

Obviously the patient is admitted if for any reason we plan to use general anesthesia. For diagnostic endoscopy we admit children almost always, because this permits better premedication and better control. In the anatomically difficult patient, the short, thick-necked individual, we generally admit the patient, especially for direct laryngoscopy, or esophagoscopy. The patient who is apprehensive and nervous can be much better managed if admitted and allowed to rest in bed before and after the procedure. Obviously, elderly and debilitated people should be admitted, as well as patients with fever or recent hemorrhage. As for foreign bodies, all depends on the nature and location of the foreign body, and more especially the patient's present condition. If there is any threat of dyspnea, of course the patient should be admitted.

The author has never done endoscopic procedures in the office though he believes that an office may be so equipped that it is perfectly safe and appropriate to do some endoscopic procedures in it, just as minor surgery is done.

A simple questionnaire was sent out to the other bronchoscopic clinics in Philadelphia and the replies disclose some differences, but many similarities in opinions. All answered "No" to the question, "Do you think that patients should always be hospitalized for endoscopic procedures?" Several of my correspondents stated that they thought patients should always be hospitalized for their first endoscopy. One stated that he thought the patient should always be in the hospital for 24 hours for a first esophagoscopy. One thought that foreign body patients should always be hospitalized, another that if biopsy was contemplated admission was advisable.

Other indications mentioned were those that I have cited previously: the debilitated patient, presence of obstruction, use of general anesthesia, etc.

All seven of my correspondents replied in the negative to the question, "Do you ever perform peroral endoscopic procedures in your office?"

CONCLUSION

The speaker's own views on the advisability of admission of patients for peroral endoscopic procedures have been expressed, and the results of a questionnaire survey of the other Philadelphia clinics has been presented. It is hoped that this presentation will stimulate expression of the views of other members of the Association.

3401 N. BROAD ST.

Abstracts of Current Articles

EAR

Similarities Between Hearing and Skin Sensations

This article summarizes Békésy's present work in skin responses and points out several similarities to auditory sensations. (One previous detailed paper on this subject has been reviewed in this column: 67:1228, 1958.) Békésy's interest in skin sensations dates back to publications of his, on vibratory sensations, as early as 1939. He had hoped (and the present paper bears him out in this respect) that the skin would permit him to observe neural aspects of vibratory responses which cannot be studied in the ear because of its relative inaccessibility.

Békésy's concept of traveling waves in the stimulatory process of the cochlea does not need any comment. It is perhaps not commonly known, however, that traveling waves are also observed on the skin, concentric to and centrifugal from the point where a point-shaped vibrator is placed. And yet the sensation is felt only under the vibrator, the place of maximal amplitude.

The "loudness" increment of the skin sensation depends upon the density of innervation which is known to differ in various skin regions. This finding bears a remarkable resemblance to the auditory phenomenon of recruitment. This entire problem was the subject of the technical paper reviewed earlier in this column.

Békésy then reports on his large cochlear model which many readers may remember from his paper and subsequent demonstration at the 1955 Academy meeting. This model is 30 cm long and contains one "perilymphatic scala" only. Its upper edge vibrates in the same way as the basilar membrane, that is, it forms traveling waves over a range of two octaves. If one places the fore arm on this model one feels a sensation in a very narrow section only, although the membrane is vibrating over a much larger area. The place of maximal sensation alters with frequency in exactly the same manner as in the ear. Even brief pulses, two cycles in duration, are localized at their

"correct" position, corresponding to their frequency. This is the direct counterpart of the same observation in the human ear which perceives a definite pitch sensation from as few as two cycles of a given frequency.

The obvious suppression of small-amplitude vibrations observed in this model led to a systematic study of inhibitory effects. Békésy differentiates two types of neural inhibition: one in which stimuli are suppressed which are delayed in time with respect to a stronger one; and another in which the sensation of the place of maximal amplitude is enhanced at the expense of the lateral spread when all stimuli are presented at the same time.

The bilateral phenomenon of directional hearing lends itself to a pertinent study on this subject: two models of the kind described above, when suitably stimulated, provide a test subject with the same sense of direction as that obtained from his two ears. There is one significant difference, however, between skin and ear which became apparent when two vibrators were placed a certain distance apart on the same skin area. As the time delay approached zero and the sensation fused and moved into the region between both stimulators (corresponding to the "midline sensation" in hearing) the area of sensation grew larger. No such increase in volume is observed in hearing. From additional evidence it is concluded that this phenomenon occurs when there is little neural interaction between the two sites of stimulation. Between the two ears, however, this interaction is probably very strong, a view which is supported by histological evidence.

The subject of inhibition and summation of spatially distributed stimuli was further studied with the aid of special rod-shaped vibrators which were in contact with the skin over their entire length. If a unidirectional, slow-acting pressure was applied, it was felt over the entire area covered by the rod. However, in response to a brief tapping of the device (the equivalent of an audible "click") the sensation was concentrated in the region of the center. Now a series of five independent vibrators mounted in one row was pressed against the skin. When all vibrators were adjusted for equal sensation magnitude (although they were tuned to different frequencies in octave intervals) only the middle vibrator was felt with its corresponding frequency but with increased magnitude.

Békésy feels that the word "Inhibition" does not fully describe these phenomena because of the contribution of the suppressed (lateral) sensations to the magnitude at the center. To indicate this

latter contribution, he prefers the term: "Funneling." The best known example of funneling action is the law of contrast in vision as first described by E. Mach. Analog sensations were produced on the skin by special stimulating devices. Furthermore, the addition of a series of clicks to a continuous sinusoidal vibration produced a strong funneling action as did a time delay between two separate vibrators.

In concluding, the various similarities are re-emphasized. The fact that the sensitivity of the skin along the arm alters from the fingertip, where it is large, to the shoulder, where it is small, lends itself to an illuminating comparison between thresholds, representation along the cerebral cortex, equal loudness contours, and magnitude of sensation area.

At the end, Békésy raises the question of significant differences between the ear and the skin (one has already been reported above). Since the organ of Corti is evolved from outer skin but is much more highly differentiated, he feels there should be functions in which the ear excels over the skin

It is impossible in a brief review to give a complete account of this work. Békésy's own paper is a "review" which should be studied in the original by everyone interested in neural aspects of Audition.

TONNDORF

The Relation Between Otitis Media and Adrenal Gland

Kunimi, M.: J. Oto-rhino-laryng. Soc. Japan. 61:1655 (Oct.) 1958.

The relation between otitis and the adrenal gland was clinically and experimentally studied. Thorn's test was done in 60 cases (30 adults and 30 children) with catarrhal otitis media. Experimental acute otitis media was produced in healthy rabbits and adrenalectomized rabbits, and serum protein fractions were studied by the salting-out method. The results were summarized as follows:

1) The function of the adrenal cortex in 60 patients (30 adults and 30 children) with catarrhal otitis media was examined by the Thorn's test. Twenty-nine patients (12 adults and 17 children) or 48% of the cases showed positive reaction. Twenty-three cases (8 adults and 15 children) out of 29 positive cases were considered to be of allergic nature. In the positive group, 9 cases (31%) recovered

from the disease; and in the negative group, 70% (or 22 out of 31 patients) showed recovery. It is considered, therefore, that the healing tendency is much slower in patients with hypofunction of the adrenal cortex, regardless of whether the nature of the disease is allergic or not.

2) The injectoin of egg albumin solution or bacterial suspension into the tympanic cavity of healthy rabbits produced suppurative otitis media. The injection of egg albumin solution or bacterial suspension into the tympanic cavity of a rabbit which had been previously sensitized with egg albumin produced allergic otitis media. The former was characterized by the proliferation of the connective tissue and cellular infiltration in the mucosa. The latter was characterized by edematous swelling, dilatation of blood vessels, hemorrhage, fibrin formation, and eosinophil infiltration. Pathologic changes in allergic otitis media were milder in the rabbit than in the guinea pig. It is considered that the manifestations of allergic otitis media vary with animal species.

3) Experimental suppurative and allergic otitis media was produced in the same manner in unilaterally adrenalectomized rabbits. In purulent otitis media, the mucosa was characterized by marked vascular dilation, slight edema, hemorrhage, and fibrin formation. In allergic otitis media severe edema, vascular dilatation, hemorrhage, and fibrin formation were remarkable.

4) In the third group, the injection of adrenal cortex hormones (Interenin) produced mucosal changes similar to those of the second group of healthy rabbits, but did not recover to normal.

5) Serum protein fractions were studied by the salting-out method. In the experimental otitis media in the non-sensitized group, a decrease of serum albumin and an increase of γ-globulin were observed. In the sensitized group, the changes in serum protein fraction were prominent. The removal of the adrenal gland was, in most cases, associated with an increase of γ-globulin, and this was more prominent in the sensitized rabbits. The injection of the adrenal cortex hormones (Interenin), to the adrenalectomized rabbit, resulted in a slight decrease of γ-globulin. The intense allergic reaction in the mucosa of the adrenalectomized rabbits was considered to be due to remarkable increase of γ-globulin which facilitates the allergic manifestations.

6) In summarizing the experimental results, it is evident that development of otitis media is closely related to the adrenal cortical

function.   Hypofunction of the adrenal cortex predisposes the animal to the development of otitis media, and once it has developed, makes the pathologic changes severe, and recovery difficult.

<div align="right">HARA</div>

Studies on the Prophylactic Effect of Vitamin B₁ on Acoustic Trauma

Ando, M.: Otologia, Fukuoka. 4:412 (Oct.) 1958.

On the basis of Sawada's test which shows the lack of Vitamin B_1 in the urine, thirty-nine males were divided into groups I to IV according to the reaction, as 2 plus, 1 plus, plus-minus, and minus.

To groups I and III, daily doses of 10 mg and 3 mg of Vitamin B_1 were given orally for 20 days.   Groups II and IV were used as controls.   All groups were exposed to white noise (110 phons for 10 minutes).

Studies revealed that Vitamin B_1 showed prophylactic effect on acoustic trauma (especially for higher tones) and lessened auditory fatigue.   Furthermore, the effect of Vitamin B_1 on the autonomic nervous system of the persons who were exposed to white noise was discussed.   Studies were made on the effect of Vitamin B_1 on acoustic trauma by examining ribonucleic acid in the spiral ganglion cells and by Pryer's reflex in guinea pigs.

<div align="right">HARA-KUROZUMI</div>

NOSE

Malignant Granuloma of the Nose

Sawashima, M., *Muto*, J., and *Sato*, M.: J. Oto-rhino-laryng. Soc. of Japan 61: 1692 (Oct.) 1958.

Sawashima and his associates present four cases of malignant granuloma of the nose.   In three of the cases the initial symptoms were nasal blockage and discharge.   Swelling and edema followed in the turbinate, eye lids, nasal mucosa or the affected areas of the face.   Ulceration usually followed in the later stage of the disease.

All cases were given irradiation but eventually in each case autopsy revealed metastasis to distant organs such as the lymph nodes,

intestines, lung, kidney, testicle, liver, spleen, and myocardium. In all cases, the affected tissue showed malignant neoplastic cells, of reticulo-endothelial origin, but different from those seen in reticulo-sarcoma. There was no evidence of allergic reaction. These 4 cases were thought to belong to a peculiar type of reticulosarcoma with tendency to necrosis.

Hara-Tsugawa

Branchiogenic Carcinoma

Strong, M. Stuart, and *Sommers, Sheldon C.:* A.M.A. Arch. Otolaryng. 68:764-769 (Dec.) 1958.

Very few diagnoses of branchiogenic carcinoma can be upheld, in the opinion of the authors and they cite Martin's doubt that such a diagnosis should ever be made. Martin feels the only adequate proof of a true branchiogenic carcinoma can be the demonstration of cancer arising in the wall of a branchial cyst. The authors continue to cite other authors, however, who leave no doubt that primary carcinoma arising in a branchial cyst does exist. They agree that the diagnosis of branchiogenic carcinoma should not be made except in cases in which there is both gross and microscopic evidence of a true branchial cyst and carcinoma is found within the cyst wall.

They present two cases which they found unusual as well as interesting. In one a branchiogenic carcinoma occurred in association with a carcinoma at the base of the tongue and in the other with a laryngeal carcinoma. They find this explicable on the grounds of the known propensity of mucosa arising from one or more of the pharyngeal pouches to develop multiple cancers.

The first patient was a 59 year old white woman who had had a painless lump present on the left side of her neck for 6 weeks. A smooth, well-defined, elastic swelling measuring about 4 cm in diameter was found anterior to the anterior border of the left sternomastoid muscle. A very small, inconspicuous 0.5 cm ulcer was situated at the junction of the base of the tongue and the left lateral wall of the pharynx immediately adjacent to the tip of the epiglottis; the ulcer was markedly indurated on palpatoin. A tentative diagnosis of carcinoma of the base of the tongue with cervical metastasis was made. Biopsy of the ulcer showed epidermoid carcinoma, grade II, in association with a large number of lymphatic cells. External radiation (3000 r) was given and resulted in the complete obscuring of the primary ulcer by edema and radiation reaction but the cervical

lesion showed no signs of regression but rather continued to slowly increase in size. No other cervical nodes were palpable. A biopsy excision of the cervical mass was done.

At operation a pale, smooth, well-encapsulated tumor was found anterior to the anterior border of the sternomastoid muscle. When the excised mass was opened, a large quantity of opalescent, straw-colored fluid escaped, leaving a thin-walled, collapsed cyst. Histologic examination revealed this was not a lymph node but a branchial cyst with several nests of epidermoid carcinoma in the wall. These malignant cells appeared to have no connection with either the outside or inside of the cyst wall. The diagnoses in this case included in addition to the primary lymphoepithelioma of the base of the tongue, also a primary branchiogenic carcinoma.

The second patient was a 66 year old man who had a lump in the right side of the neck for 5 weeks. The mass was excised and histologic study showed a thin-walled cyst lined by squamous epithelium; the cyst was clearly of branchial origin. At one point the epithelium had undergone malignant change and infiltrated the wall of the cyst. A diagnosis of early epidermoid carcinoma arising in a branchial cyst was made. The patient did well for two years postoperatively, when he developed epidermoid carcinoma of the larynx, which failed to respond to x-ray therapy given elsewhere and the patient died one year later.

HILDING

THROAT

Thrush Complicating Radiotherapy of the Mouth and Neck

Cultures or direct smears or both were made of membranous lesions of the mouth developing in 7 patients receiving roentgen or cobalt 60 therapy for disease of the head and neck. All cultures were positive for C-*Albicans* and in the four cases in which direct examination of the smear was done the organism was found growing in the filamentous form in the membrane.

The demonstration that some of the classical changes of radiation mucositis are due to secondary infection is not surprising. Damage to tissue owing to irradiation plus the possible effect on the normal

mouth flora caused by changes in the secretion of the salivary glands is considered responsible, at least in part, for the pathologic overgrowth of *C-Albicans*. The secondary infection thus produced is refractory to the commonaly used oral antiseptics. Nystatin is the best drug available at present for this complication of radiation therapy.

JORSTAD

Books Received

The Middle Ear

Heinrich G. Kobrak, M.D., Ph.D., Professor of Otological Research, College of Medicine, Wayne State University. Contributors: *J. E. Fournier*, Audiologist, Compagnie, Francaise d'Audiologie, Paris, France; *John R. Lindsay*, M.D., Professor and Head of Otolaryngology, University of Chicago; *Samuel Rosen*, M.D., Consulting Otologist, Mount Sinai Hospital, New York, and Associate Professor of Otolaryngology, Columbia University; *A. Wilska*, Professor of Physiology, University of Helsinki; *H. Wullstein*, M.D., Professor of Otolaryngology, Director of Throat, Nose and Ear Clinic, University of Wurzburg; *Fritz Zoellner*, M.D., Professor of Otolaryngology, Director of Throat, Nose and Ear Clinic, University of Freiburg. Pp. x & 254, 232 figures, 7 tables and 6 colored plates. Chicago, University of Chicago Press, 1959. ($15.00)

This book reflects the sincere dedication of Heinrich Kobrak to the study of the function of the middle ear and its practical implications for better hearing. Since he desired that this be "M.D. otology" rather than a theoretical dissertation, a large part of the book is devoted to an excellent discussion of the indications and techniques for the use of acoustic protheses by the author as well as the surgical aspects of hearing rehabilitation by Doctors Wullstein, Zoellner, Rosen and Lindsay.

A large part of the book is devoted to Dr. Kobrak's investigative works. These include excellent sections on intratympanic muscle reflexes and photography of the dynamics of the tympanic membrane and ossicular chain.

For those interested in the most recent advances in tympanoplasty, this monograph offers a rich storehouse of information dealing with the indications for surgery, surgical techniques, pros and cons of various plastic procedures, etc. The chapters by Lindsay and Rosen present excellent reviews of recent developments in fenestration and stapes mobilization surgery.

It is most unfortunate that this fine contribution is marred by inferior reproduction and printing of the black and white photographs and photomicrographs which are so essential to a complete understanding of the text. Nonetheless, this fine memorial to Dr. Kobrak is recommended to all serious students of the middle ear.

Notices

CASSELBERRY PRIZE

A sufficient fund having accrued from the Casselberry Fund for encouraging advancement in the art and science of Laryngology and Rhinology, this sum is now available in part or as a whole, for a prize award. Theses must be in the hands of the Secretary of the American Laryngological Association prior to January 1 of any given year.

The Award is a prize of money with accampanying certificate signed by the officers of the American Laryngological Association. The sum of money will be agreed upon by the Council of the Association after the manuscript has been evaluated by the Award Committee. It may be awarded in whole or in part among several contestants.

Eligible contestants may be: 1. Hospital interns, residents, or graduate students in Rhinology and Laryngology; 2. An individual with an M.D. degree who is actively practicing or teaching Rhinology and Laryngology in the Americas; 3. Any scientific worker in the field of Rhinology and Laryngology.

Manuscripts shall be presented to the Secretary of the Association under nom de plume which shall in no way indicate the author's identity. There shall also be a sealed envelope bearing the nom de plume and containing a card showing the name and address of the contestant which the Secretary shall keep in his possession.

Manuscripts must be limited to 5000 words and must be typewritten in double spacing on one side of the sheet. The thesis shall not have been published elsewhere before submission.

The successful thesis shall become the property of the American Laryngological Association but this provision shall in no way interfere with publication of the thesis in the Journal of the author's choice. Unsuccessful contributions will be returned promptly to their authors.

The Award which will be made at the Annual Meeting of the American Laryngological Association shall be based on:

1.   Originality of material.

2.   Scientific and clinical value.

3.   Suitability for this Award.

4.   Method of presentation as to style,
      illustrations and references.

The maximum amount of the Award shall not exceed $200.00.

Lyman A. Richards, Secy.

Massachusetts Institute of Technology

Cambridge 39, Mass.

ACADEMY HOME STUDY COURSES

The 1959-1960 Home Study Courses in the Basic sciences related to ophthalmology and otolaryngology, which are offered as a part of the educational program of the American Academy of Ophthalmology and Otolaryngology, will begin on September 1 and continue for a period of ten months. Detailed information and application forms can be secured from Dr. William L. Benedict, the executive secretary-treasurer of the Academy, 15 Second Street S. W., Rochester, Minnesota. Registrations should be completed before August 15.

PAN-PACIFIC SURGICAL ASSOCIATION

The Eighth Congress of the Pan-Pacific Surgical Association will be held in Honolulu, Hawaii, September 28 through October 5 in 1960.

All members of the profession are cordially invited to attend and are urged to make arrangements as soon as possible if they wish to be assured of adequate facilities.

An outstanding scientific program by leading surgeons promises to be of interest to all doctors. Nine surgical specialty sections are held simultaneously.

Further information and brochures may be obtained by writing to Dr. F. J. Pinkerton, Director General of the Pan-Pacific Surgical Association, Suite 230, Alexander Young Building, Honolulu 13, Hawaii.

UNIVERSITY OF ILLINOIS
COLLEGE OF MEDICINE

The Department of Otolaryngology, University of Illinois College of Medicine, announces two special postgraduate courses to be offered in the fall of 1959:

Annual Otolaryngologic Assembly. The Assembly will be conducted September 18 through September 26, 1959, and will consist of a series of lectures and panels concerning advancements in otolaryngology. Some of the sessions will be devoted to surgical anatomy of the head and neck and histopathology of the ear, nose and throat. Guest lecturers will participate in an entire day's program reviewing the latest advances and principles of temporal bone surgery.

Chairmen of the Assembly are Maurice F. Snitman, M.D., and Emanuel M. Skolnik, M.D.

Course in Laryngology and Bronchoesophagology. The course in laryngology and bronchoesophagology, under the chairmanship of Paul H. Holinger, M.D., is scheduled November 9 through November 21, 1959.

Interested physicians should write direct to the Department of Otolaryngology, 1853 West Polk Street, Chicago 12, Illinois.

AKRON ACADEMY

The Akron Academy of Ophthalmology and Otolaryngology announces a postgraduate course in Allergy and the Endocrinological Aspects of Allergy by Herbert J. Rinkel, M.D., Kansas City, Missouri, and Z. Z. Godlowski, M.D., Associate in Medicine at Northwestern University, Chicago, Illinois, May 4-6, 1959, at the Akron City Club, Ohio Building, Akron, Ohio. A.A.G.P. credit will be given if desired. Registration fee is $35.00. For further information, contact A. L. Peter, M.D., 656 West Market Street, Akron 3, Ohio.

TEMPLE UNIVERSITY

The following postgraduate courses will be given in 1959:

Postgraduate course in Laryngology and Laryngeal Surgery, September 21 to October 2, 1959.

Postgraduate course in Bronchoesophagology, November 9 to 20, 1959.

These courses are to be given in the Department of Laryngology and Broncho-Esophagology, Temple University Medical Center, under the direction of Drs. Chevalier L. Jackson and Charles M. Norris.

The tuition fee for each course is $250. Application and further information may be obtained by writing to Jackson-Research, Lab. 604, Temple University Medical School, 3400 N. Broad Street, Philadelphia 40, Pa.

PARIS FACULTY OF MEDICINE

A course on the Technique of Audiology, organized by the Faculty of Paris, will be held on October 12-18, 1959.

For details please apply to the Secretary: Mr. J. E. Fournier, Hôpital Lariboisière, 2 Rue Ambroise-Paré, Paris X.

OFFICERS

OF THE

NATIONAL AND INTERNATIONAL

OTOLARYNGOLOGICAL SOCIETIES

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Erling W. Hanson, M.D., Minneapolis
Executive Secretary: Dr. William L. Benedict, Mayo Clinic, Rochester, Minn.
Meeting: Palmer House, Chicago, October 10-15, 1959

AMERICAN BOARD OF OTOLARYNGOLOGY

President: Dr. Gordon D. Hoople, Syracuse, N.Y.
Secretary: Dr. Dean M. Lierle, University Hospital, Iowa City, Iowa
Examination: Chicago, October 1959

AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

President: Daniel C. Baker, Jr., M.D., 903 Park Avenue, New York City, N. Y.
Secretary: F. Johnson Putney, M.D., 1712 Locust Street, Philadelphia 3, Pa.
Meeting: Deauville Hotel, Miami Beach, Florida, March 15 and 16, 1960

AMERICAN LARYNGOLOGICAL ASSOCIATION

President: W. J. McNally, M.D., Montreal, Canada
Secretary: Lyman G. Richards, Mass. Inst. Tech., Cambridge, Mass.
Meeting: Deauville Hotel, Miami Beach, Fla., March 18-19, 1960

AMERICAN LARYNGOLOGICAL, RHINOLOGICAL AND OTOLOGICAL SOCIETY, INC.

President: Dr. Theo. E. Walsh, St. Louis
Secretary: Dr. C. Stewart Nash, 708 Medical Arts Bldg., Rochester, N.Y.
Meeting: Deauville Hotel, Miami, Fla., March 15, 16, 17, 1960

AMERICAN MEDICAL ASSOCIATION, SECTION ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY

Chairman: Victor R. Alfaro, M.D., Washington, D.C.
Secretary: Walter E. Heck, M.D., San Francisco, Calif.
Meeting: Atlantic City, June 8-12, 1959

AMERICAN OTOLOGICAL SOCIETY

President: Robert C. Martin, M.D., San Francisco

Secretary-Treasurer: Lawrence R. Boies, M.D., University of Minnesota Hospitals, Minneapolis 14, Minnesota

Meeting: Deauville Hotel, Miami Beach, Fla., March 13-14, 1960

THE AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

President: Joseph W. Hampsey, M.D., Grant Bldg., Pittsburgh 19, Pa.

Secretary-Treasurer: Daniel S. DeStio, M.D., 121 S. Highland Ave., Pittsburgh 6, Pa.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: H. Leroy Goss, M.D., 620 Cobb Building, Seattle 1, Wash.

Secretary-Treasurer: Homer E. Smith, M.D., 508 East South Temple, Salt Lake City, Utah

THE SOCIETY OF MILITARY OTOLARYNGOLOGISTS

President: Lt. Colonel Stanley H. Bear, USAF (MC)

Secretary-Treasurer: Captain Maurice Schiff, MC, USN, U. S. Naval Hospital, Oakland, California

CANADIAN OTOLARYNGOLOGICAL SOCIETY

President: Dr. G. Arnold Henry, 170 St. George St., Toronto, Ontario

Secretary: Dr. Donald M. MacRae, 324 Spring Garden Road, Halifax, Nova Scotia

Meeting: Sheraton-Brock Hotel, Niagara Falls, Ontario, October 9 and 10, 1959

MEXICAN SOCIETY OF OTOLARYNGOLOGY

President: Dr. Rafael Giorgana

Secretary: Dr. Carlos Valenzuela, Monterrey 47 Mexico 7, D.F.

PAN-AMERICAN ASSOCIATION OF OTO-RHINO-LARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY

President: Dr. Jose Gros, Havana

Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa.

INTERNATIONAL BRONCHOESOPHAGOLOGICAL SOCIETY

President: Dr. Jo Ono, Tokyo

Secretary: Dr. Chevalier L. Jackson, 3401 N. Broad St., Philadelphia 40, Pa.